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(12) **United States Patent**  
**Xiao et al.**(10) **Patent No.: US 10,189,840 B2**  
(45) **Date of Patent: Jan. 29, 2019**(54) **SUBSTITUTED TRICYCLIC  
HETEROCYCLIC COMPOUNDS**

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(2018.01); **A61P 37/00** (2018.01); **C07D**  
**487/06** (2013.01)(58) **Field of Classification Search**CPC ..... **C07D 471/14**USPC ..... **514/233.2**

See application file for complete search history.

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*Primary Examiner* — Khasay Habte(74) *Attorney, Agent, or Firm* — Gary Greenblatt(57) **ABSTRACT**Disclosed are compounds of Formula (I) or a salt thereof, wherein: X is N; W is: (i)  $-(CR_3R_3)_{1-4}-$ ; (ii)  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; Or (iii)  $-Y-(CR_3R_3)_2-Y-$ ; and Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, x, and y are defined herein. Also disclosed are methods of using such compounds as modulators of TNF $\alpha$ , and pharmaceutical compositions comprising such compounds. These compounds are useful in treating inflammatory and autoimmune diseases.**9 Claims, 3 Drawing Sheets**

FIG. 1

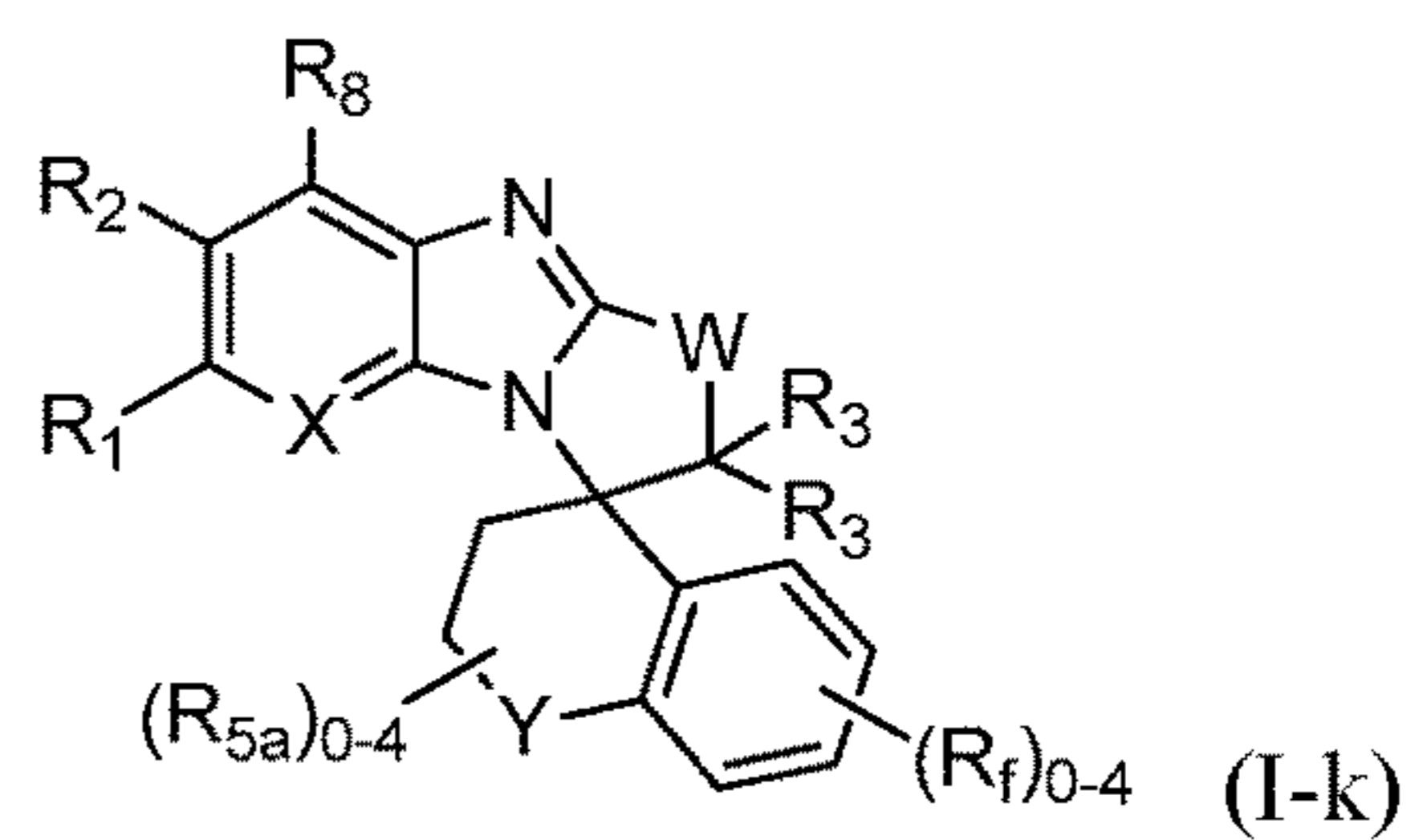
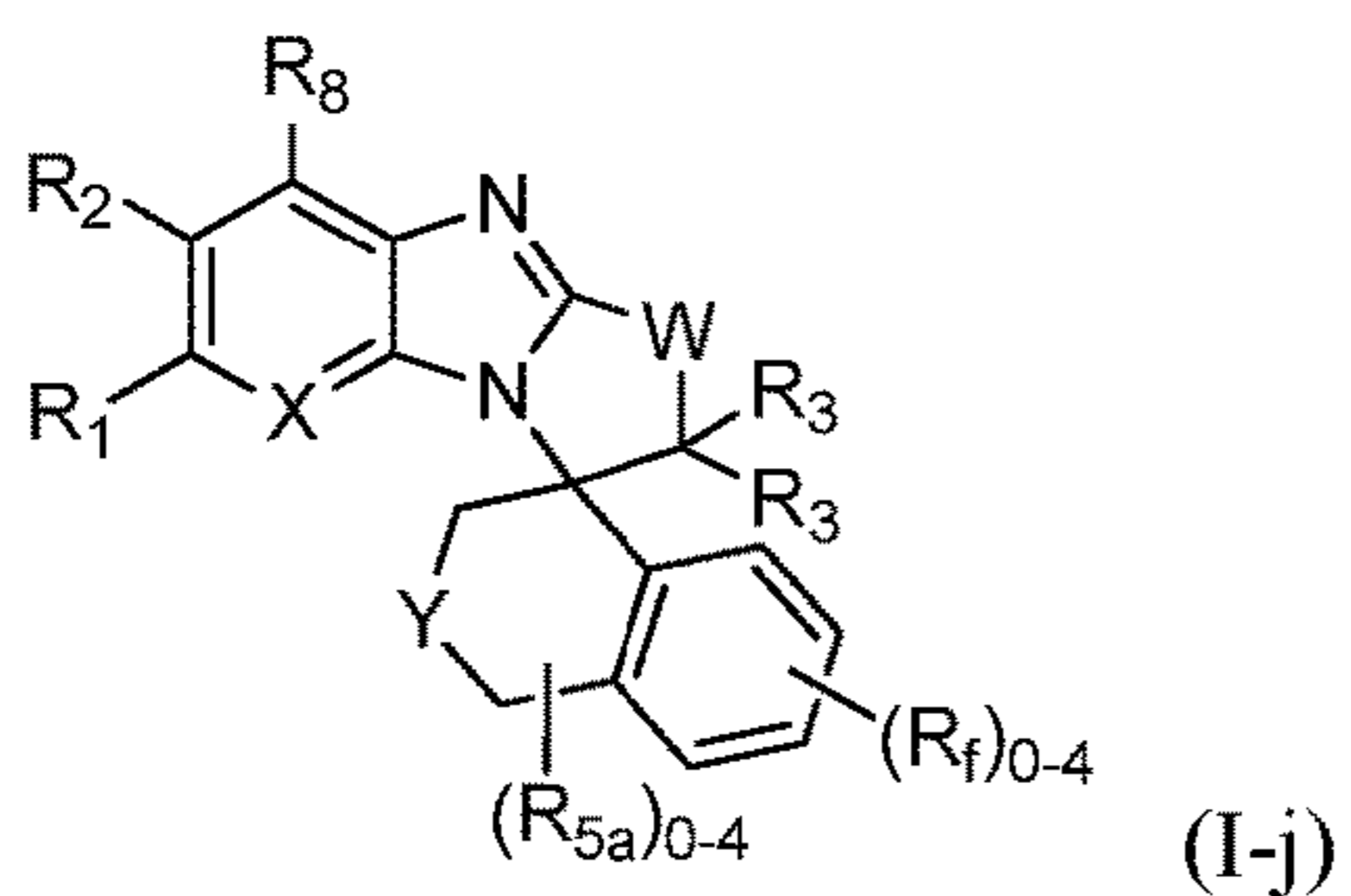
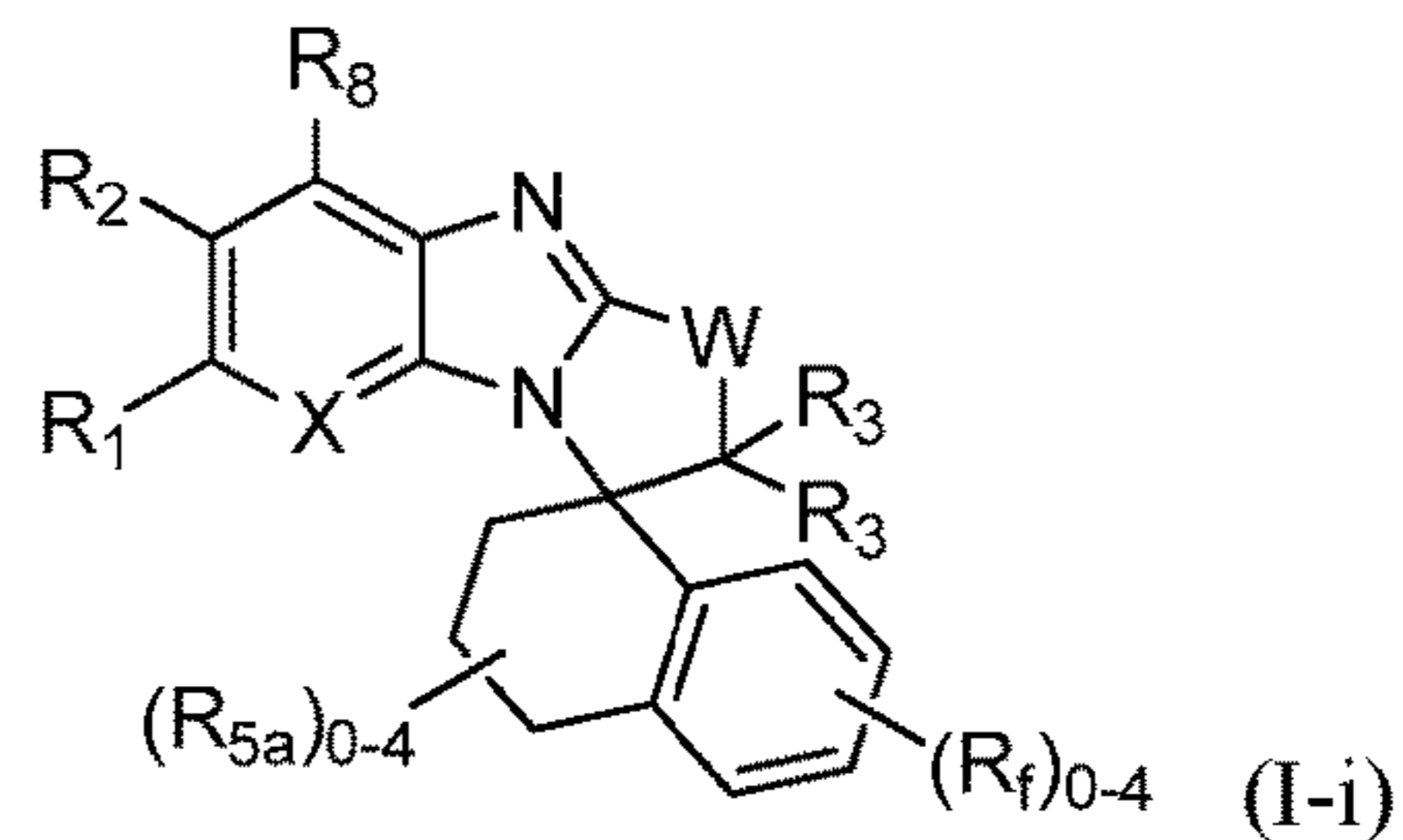
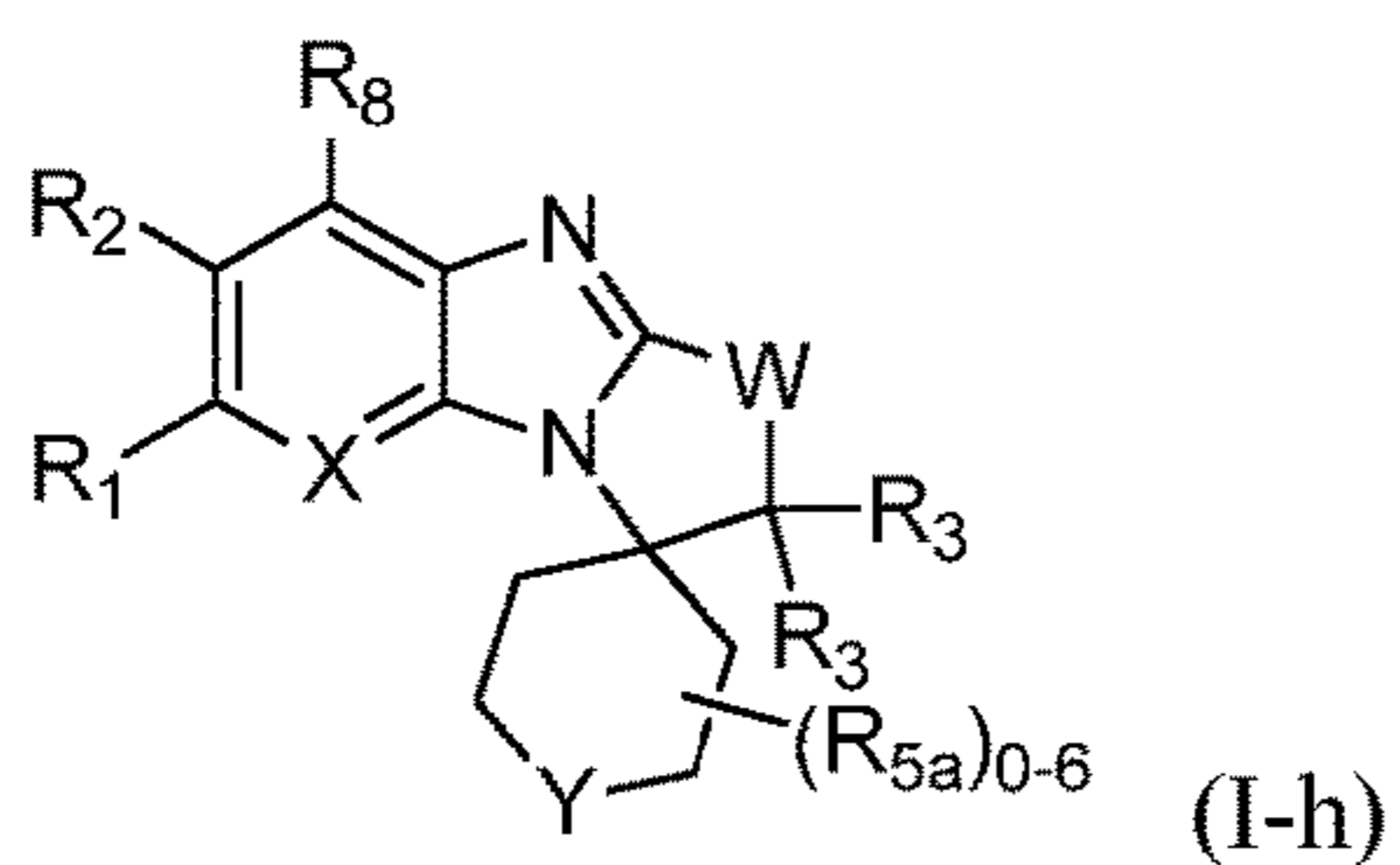
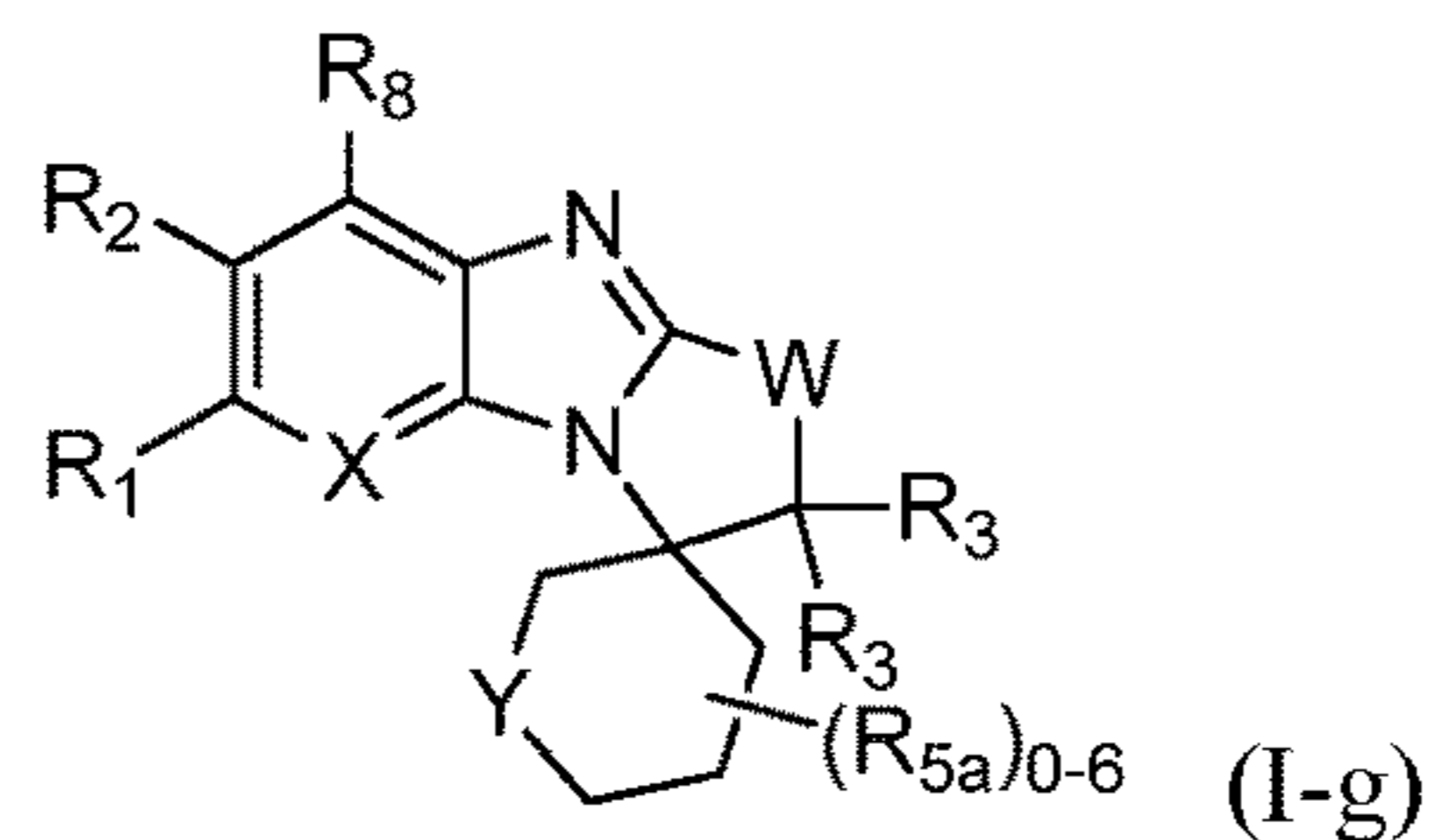
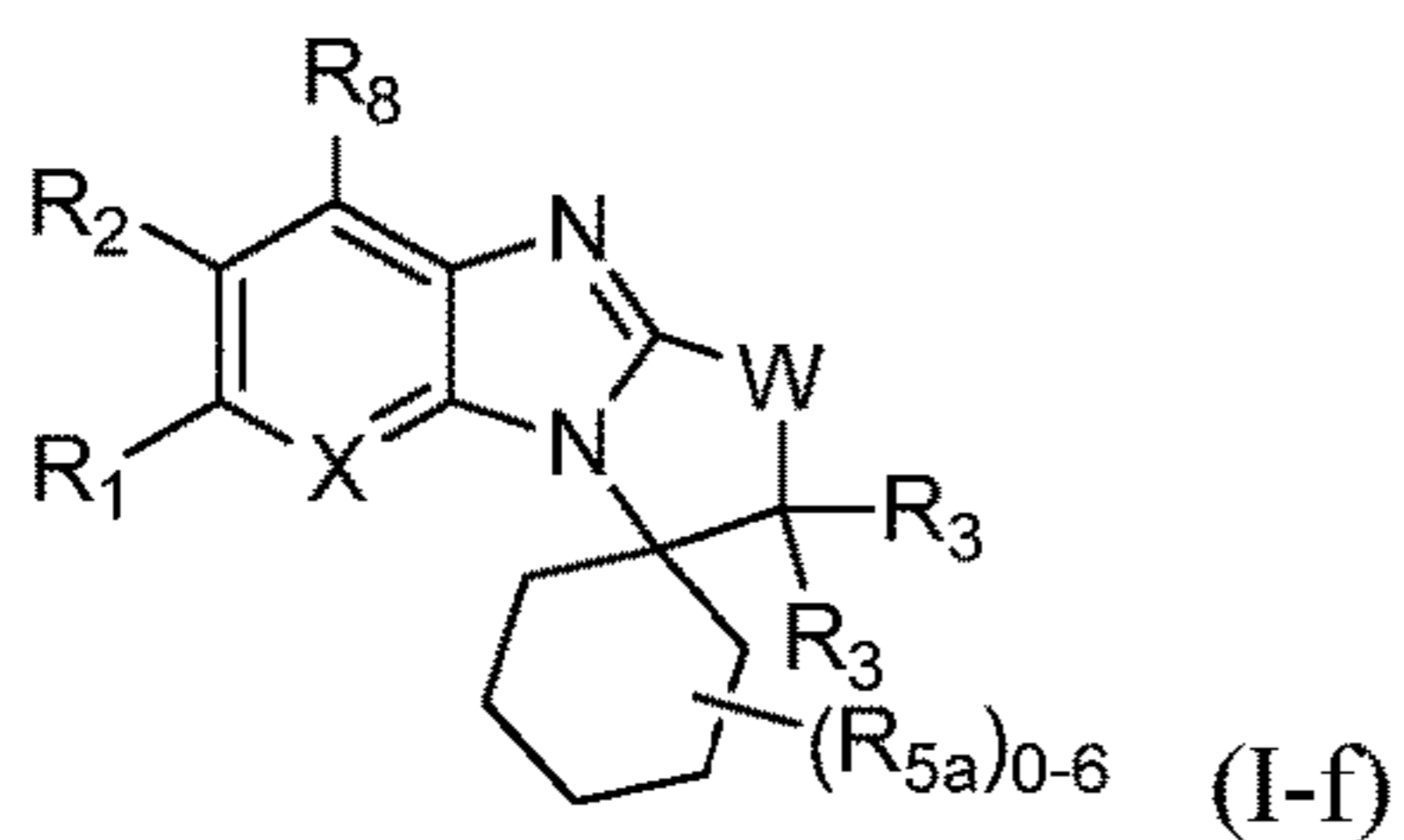
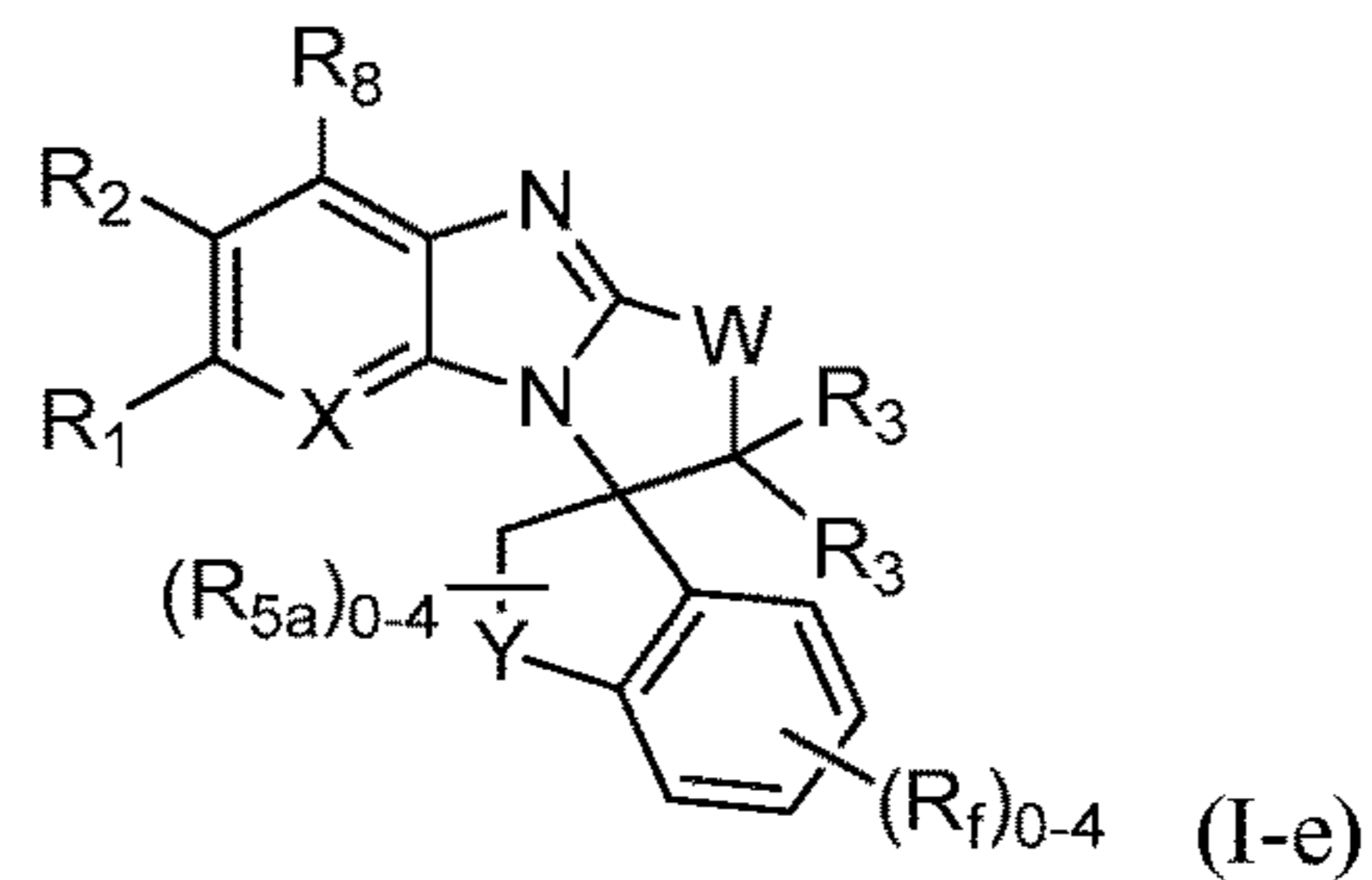
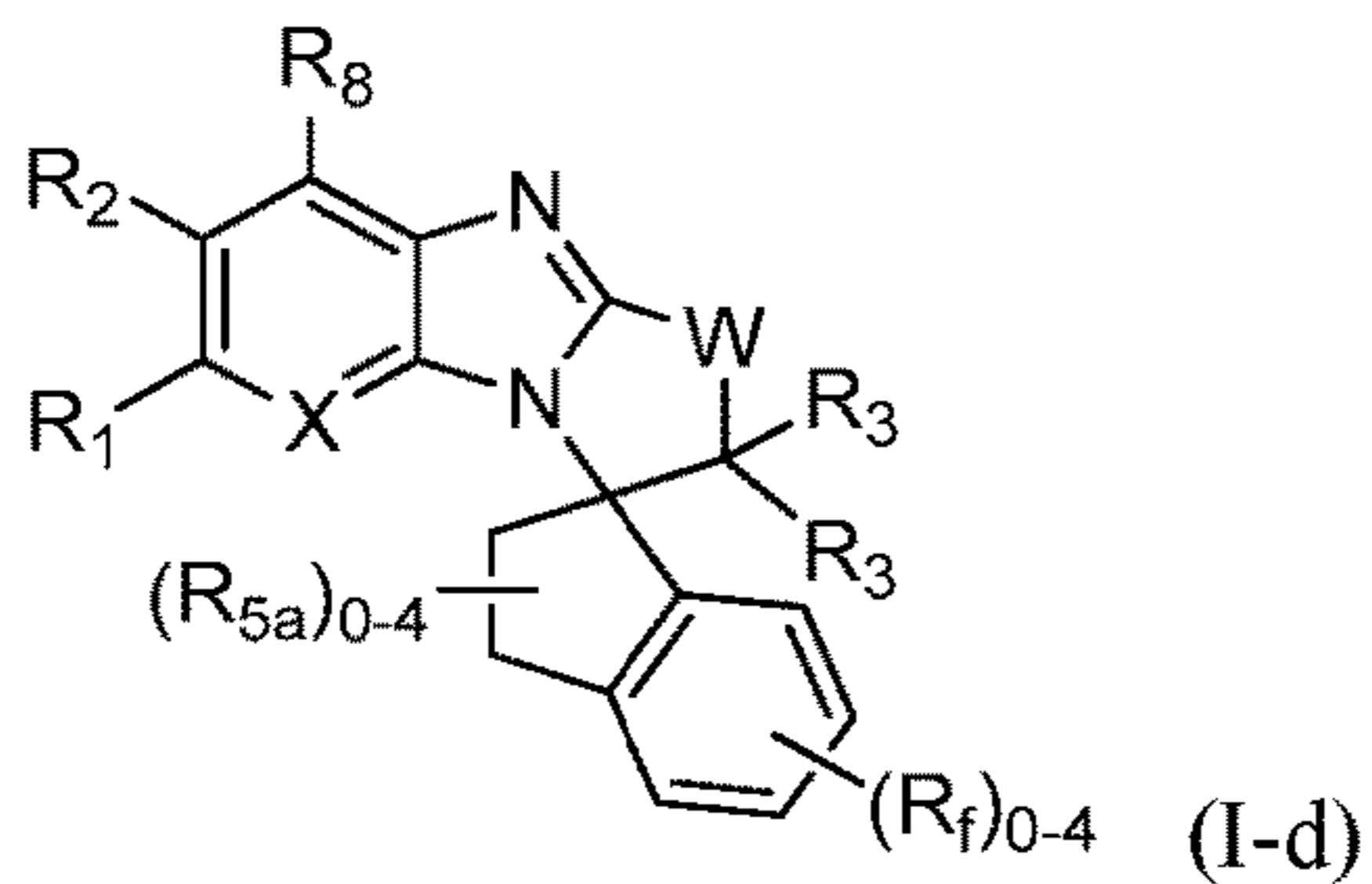
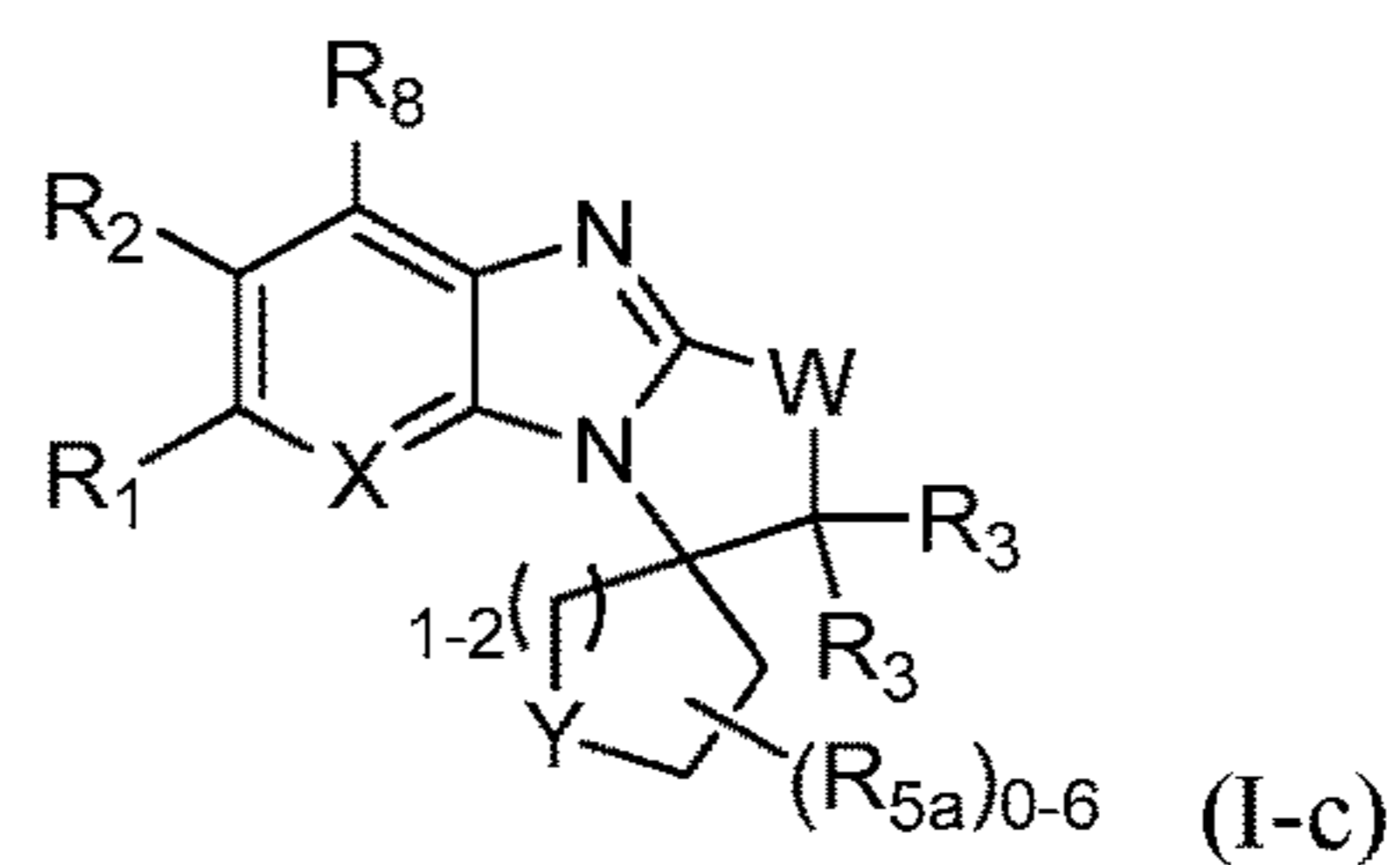
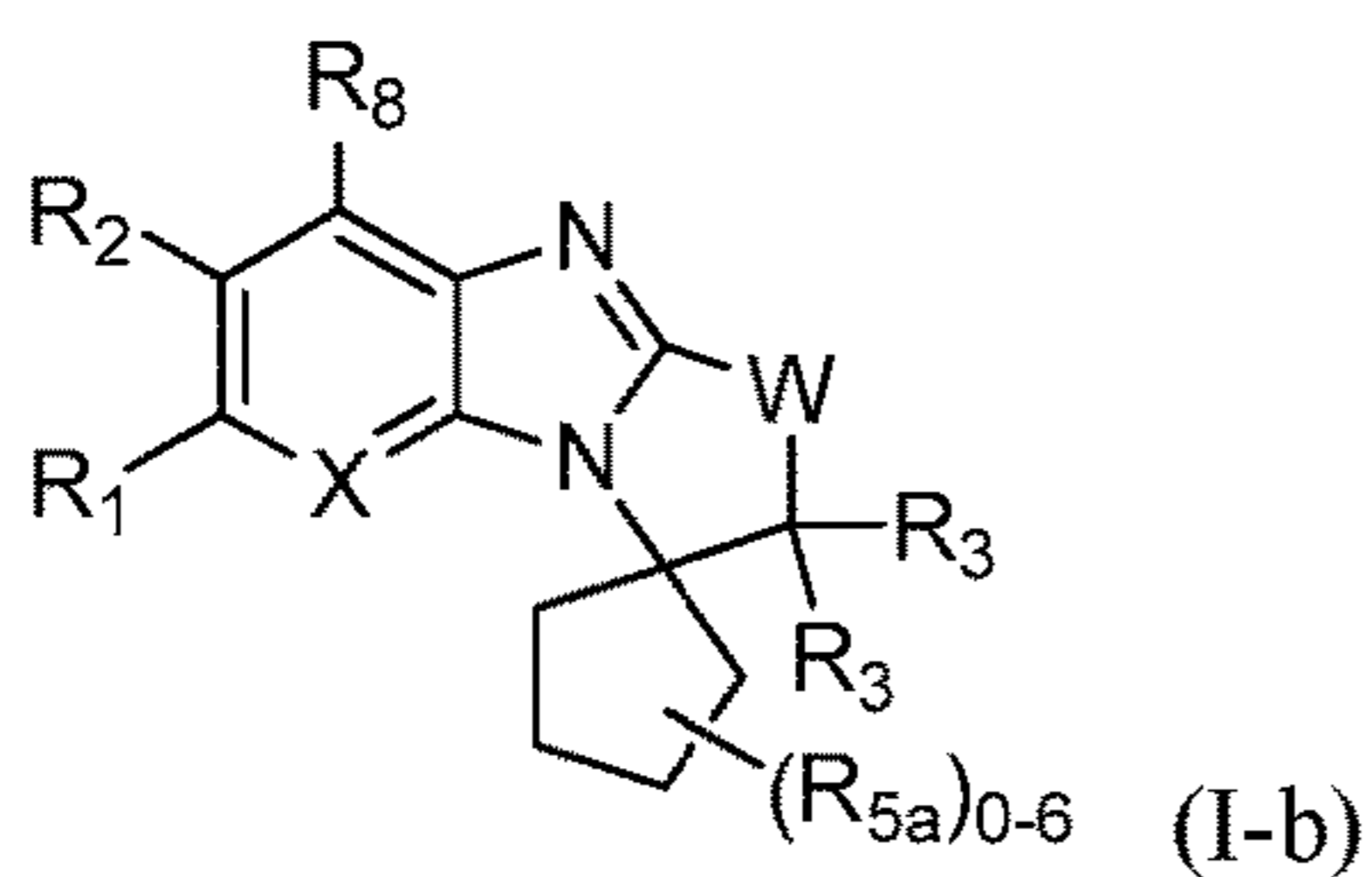
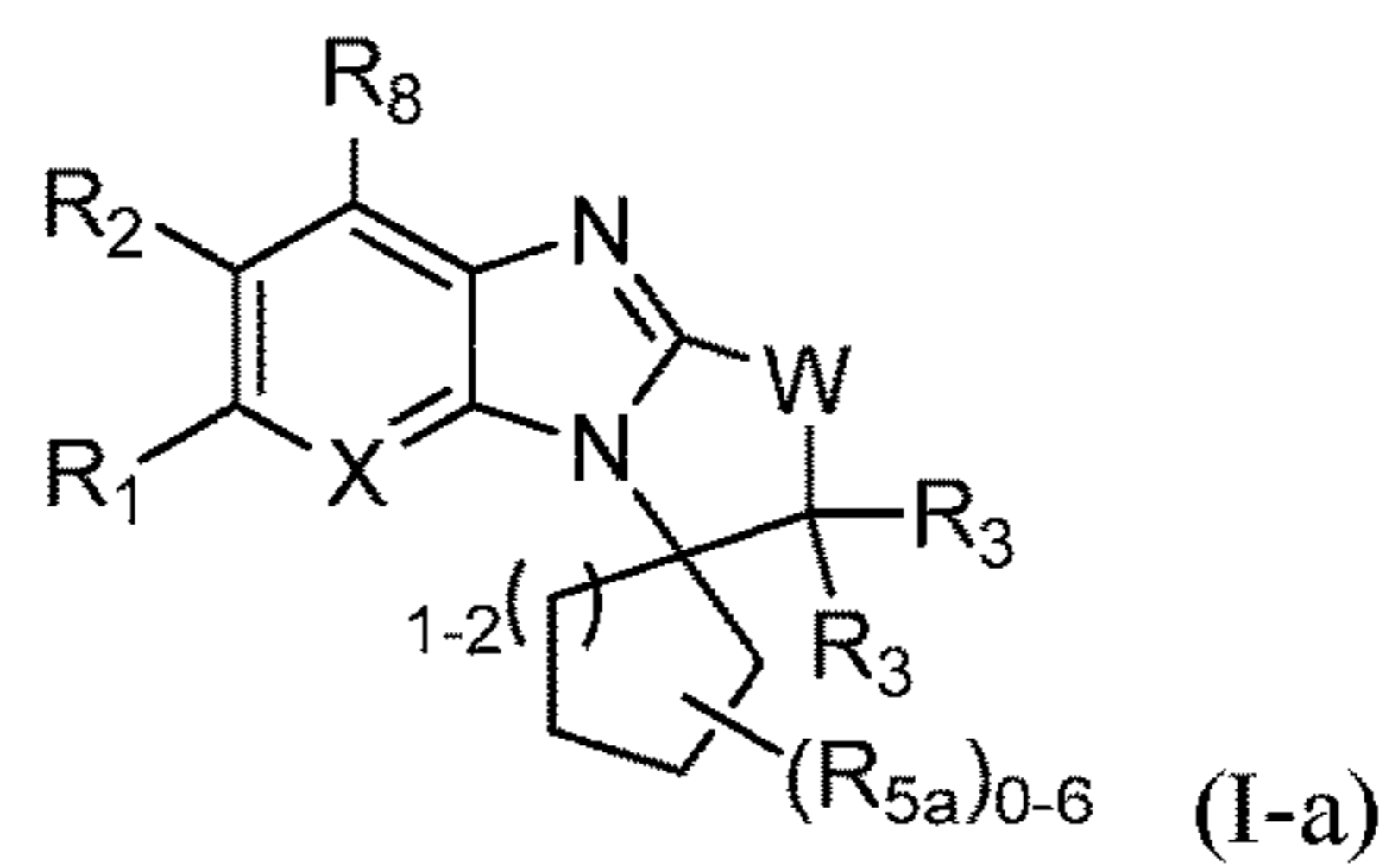
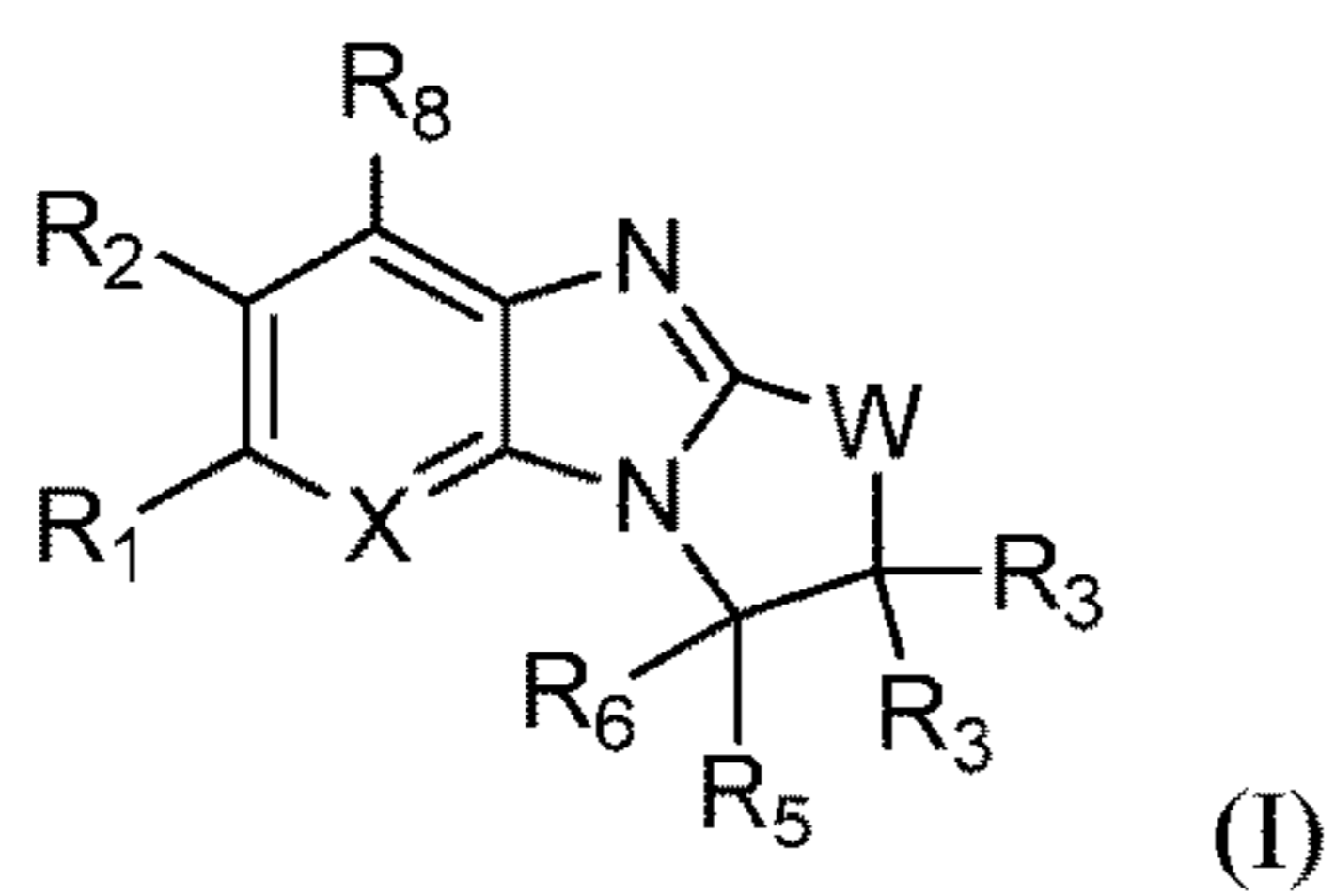


FIG. 2

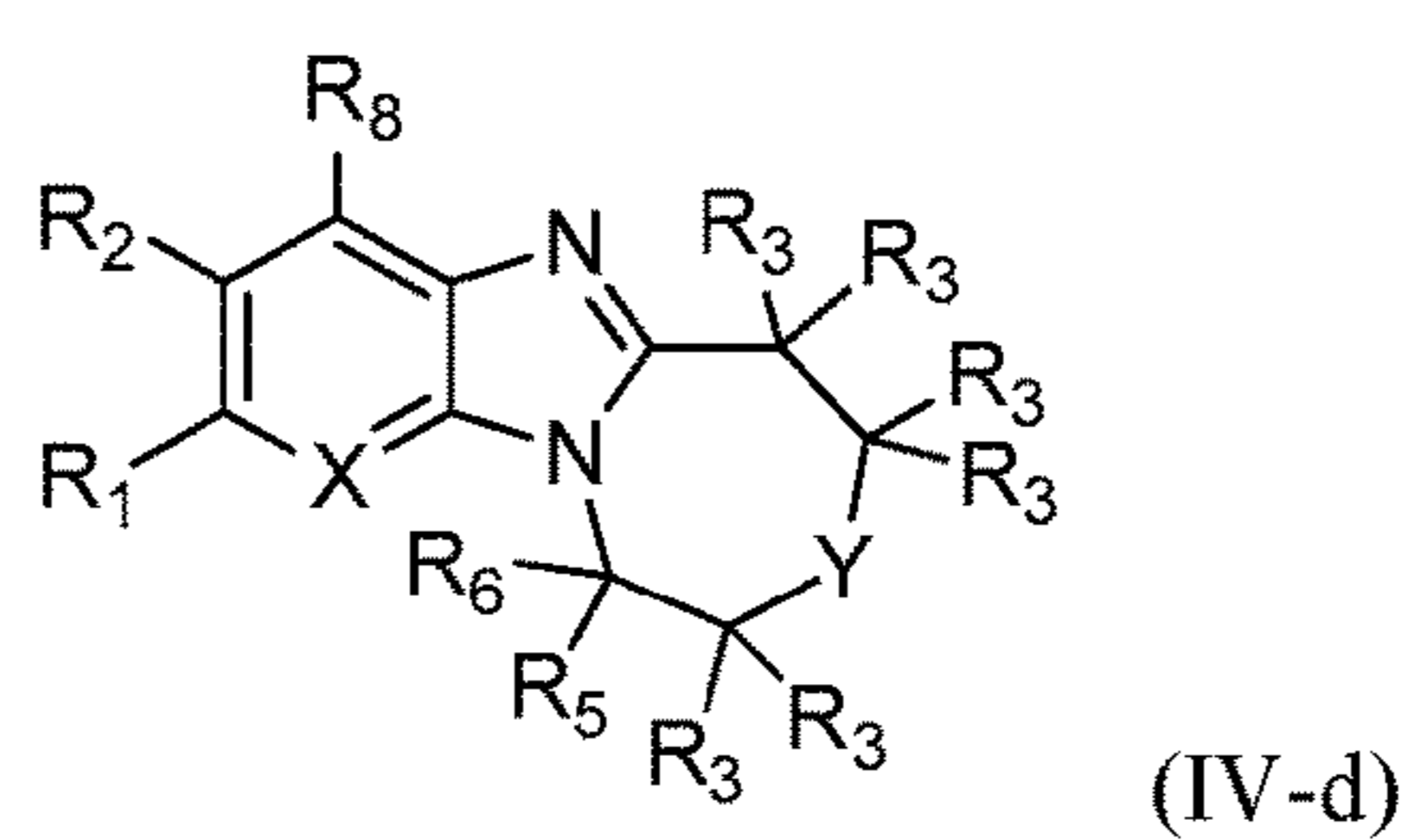
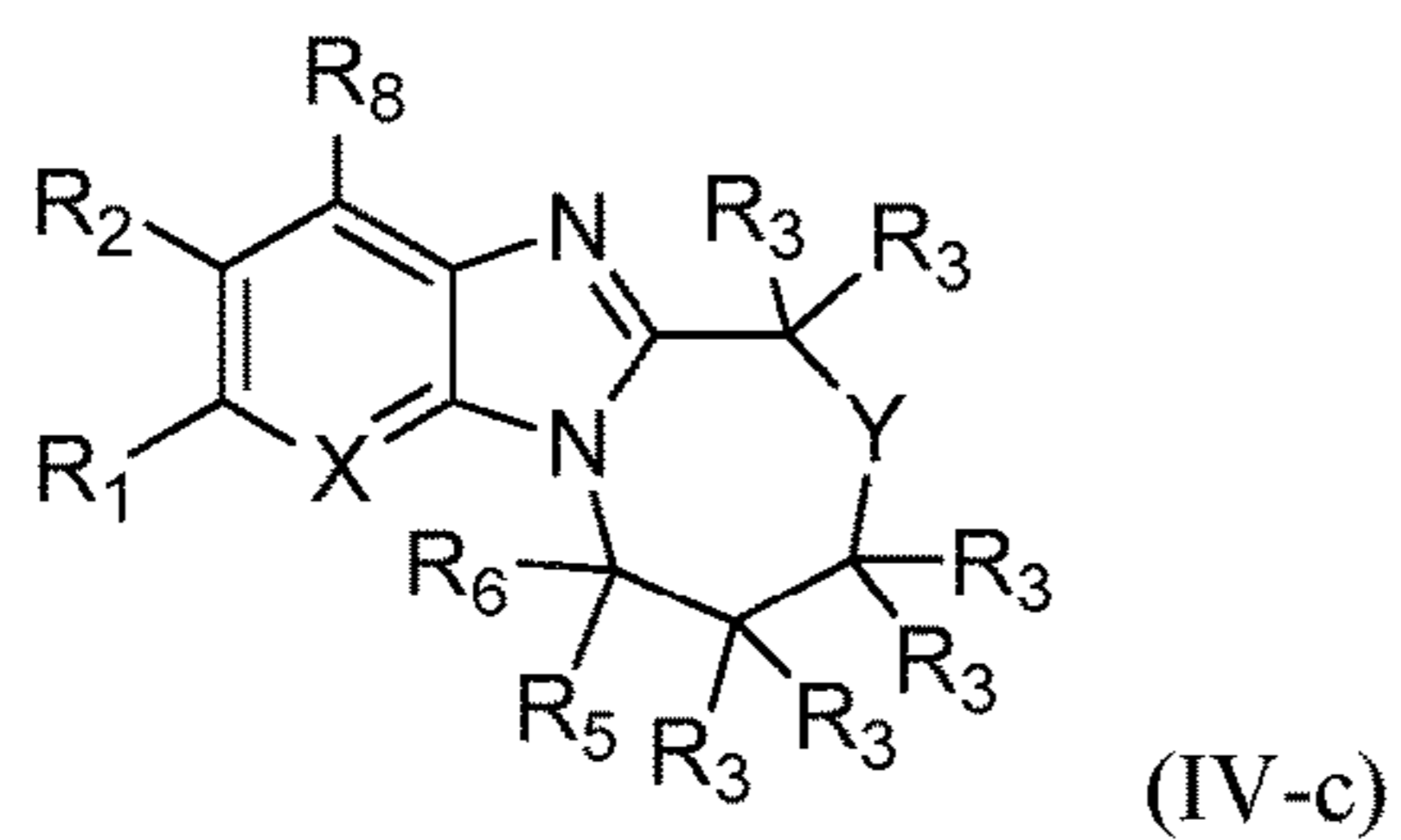
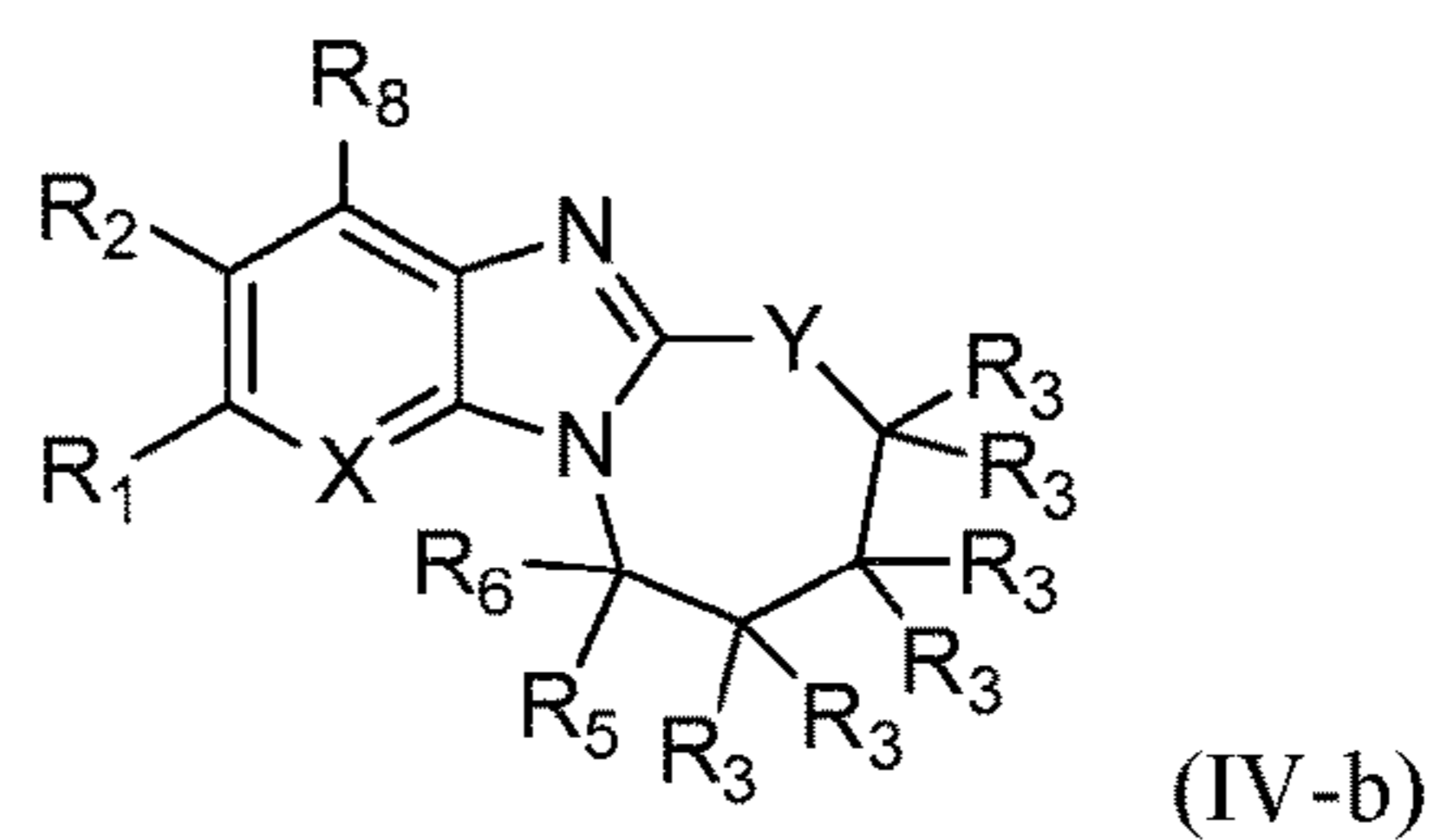
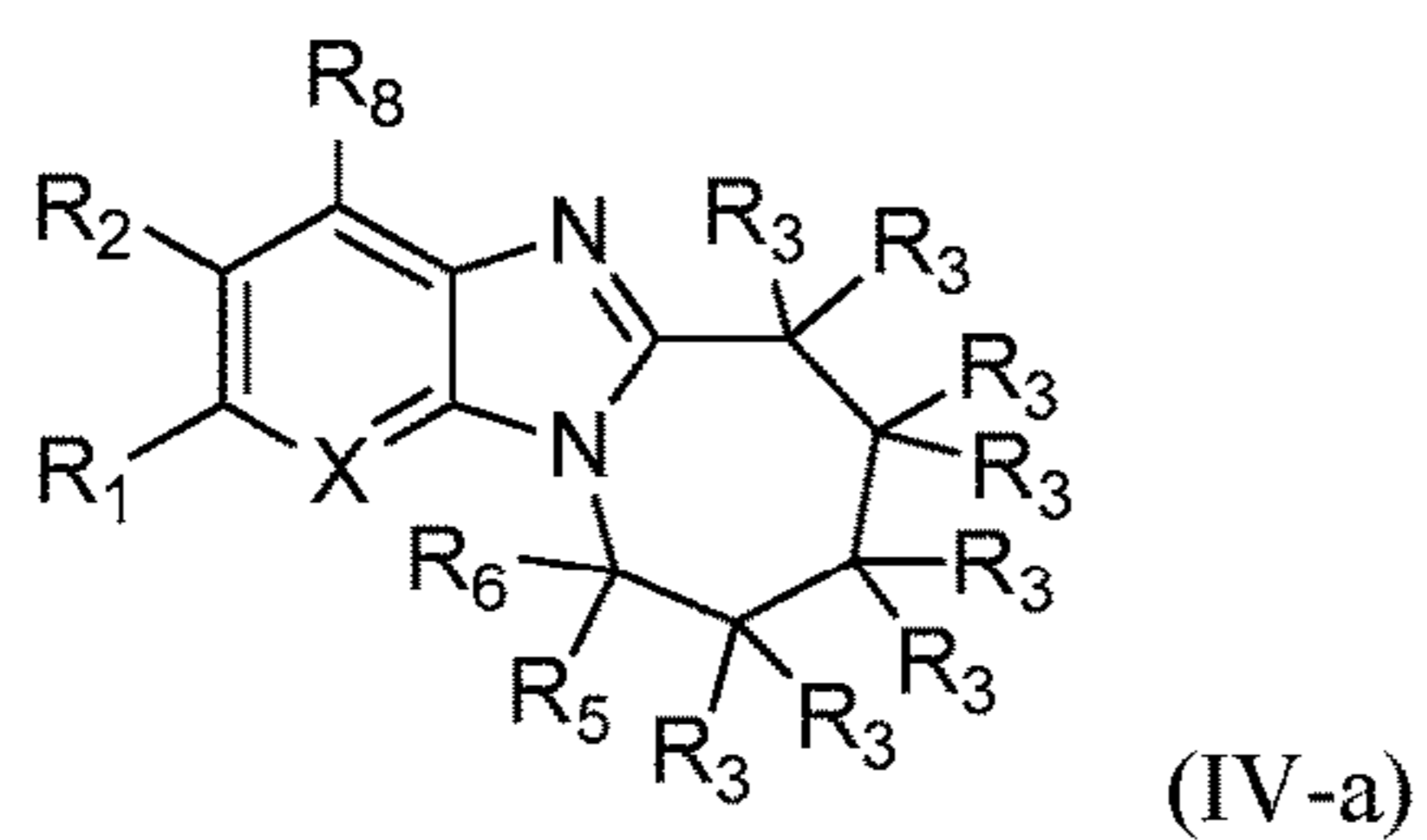
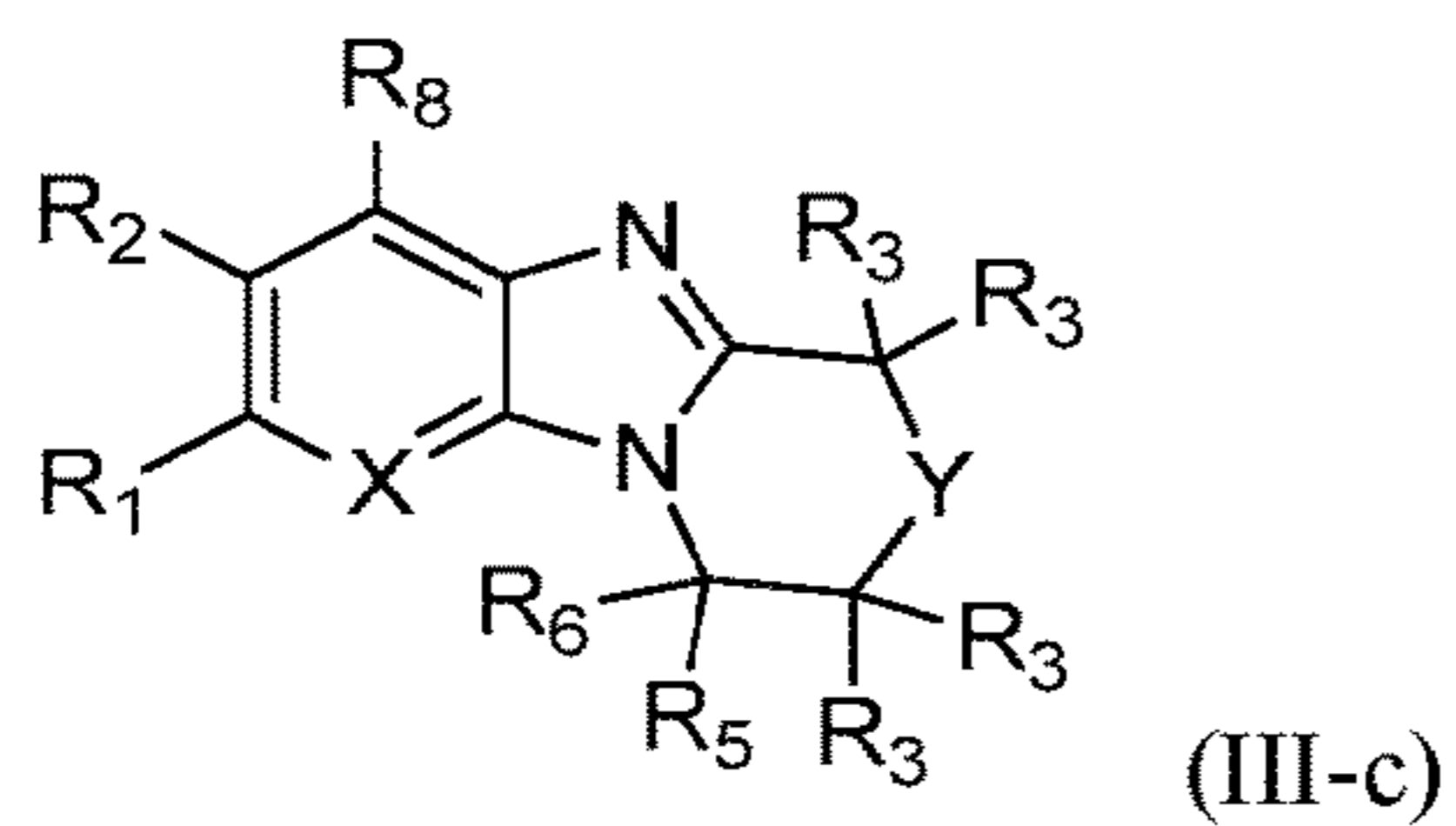
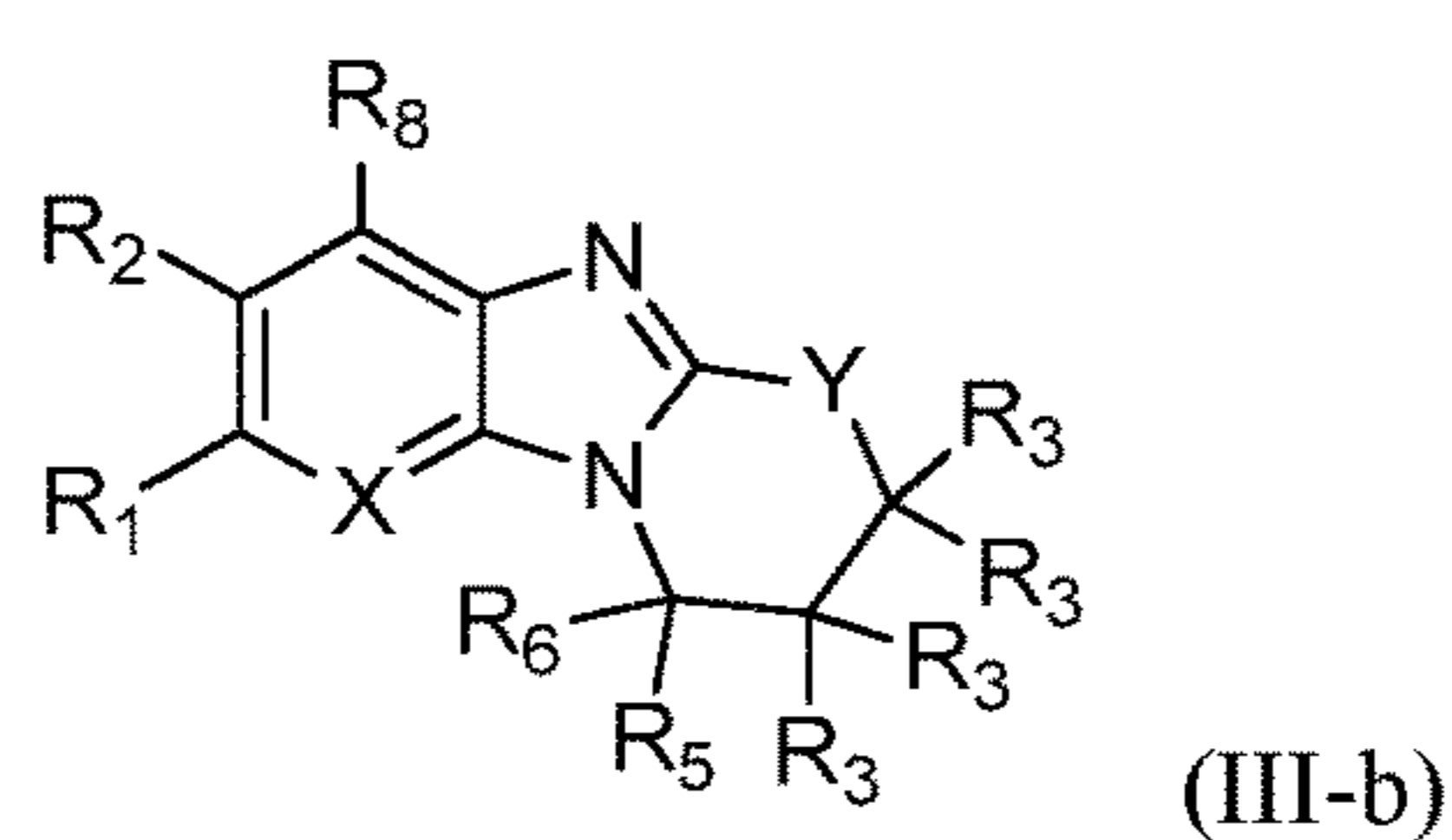
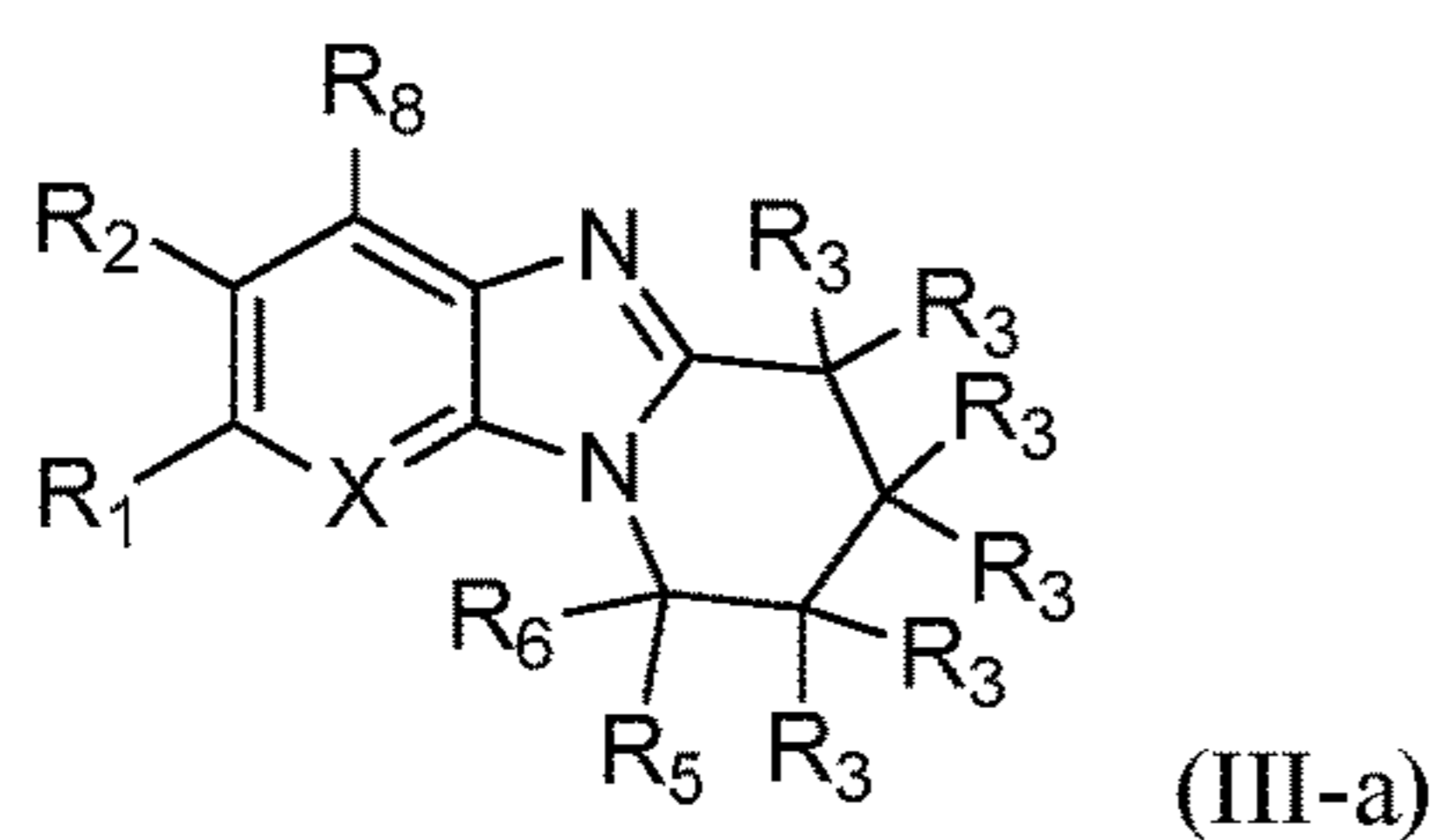
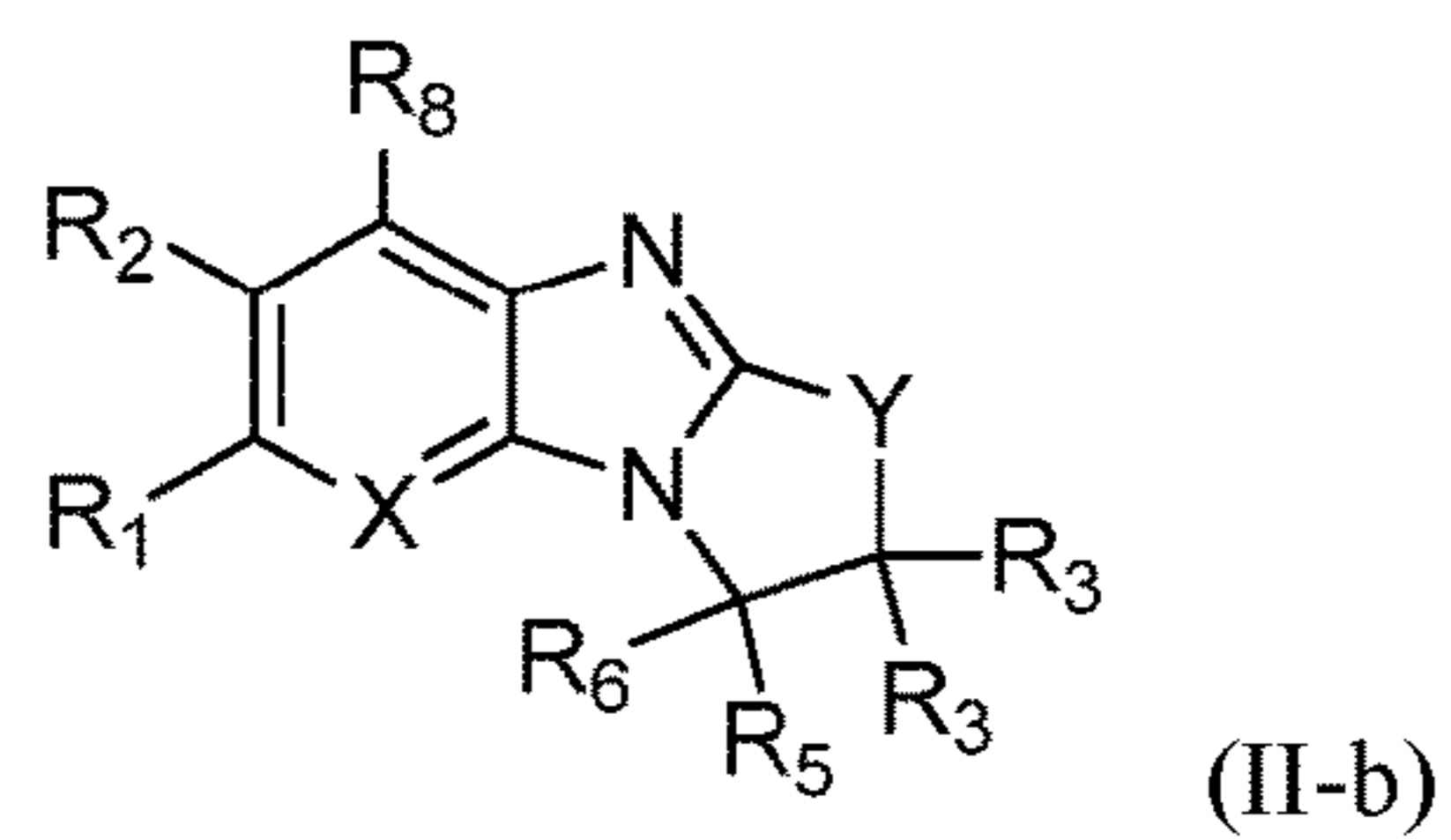
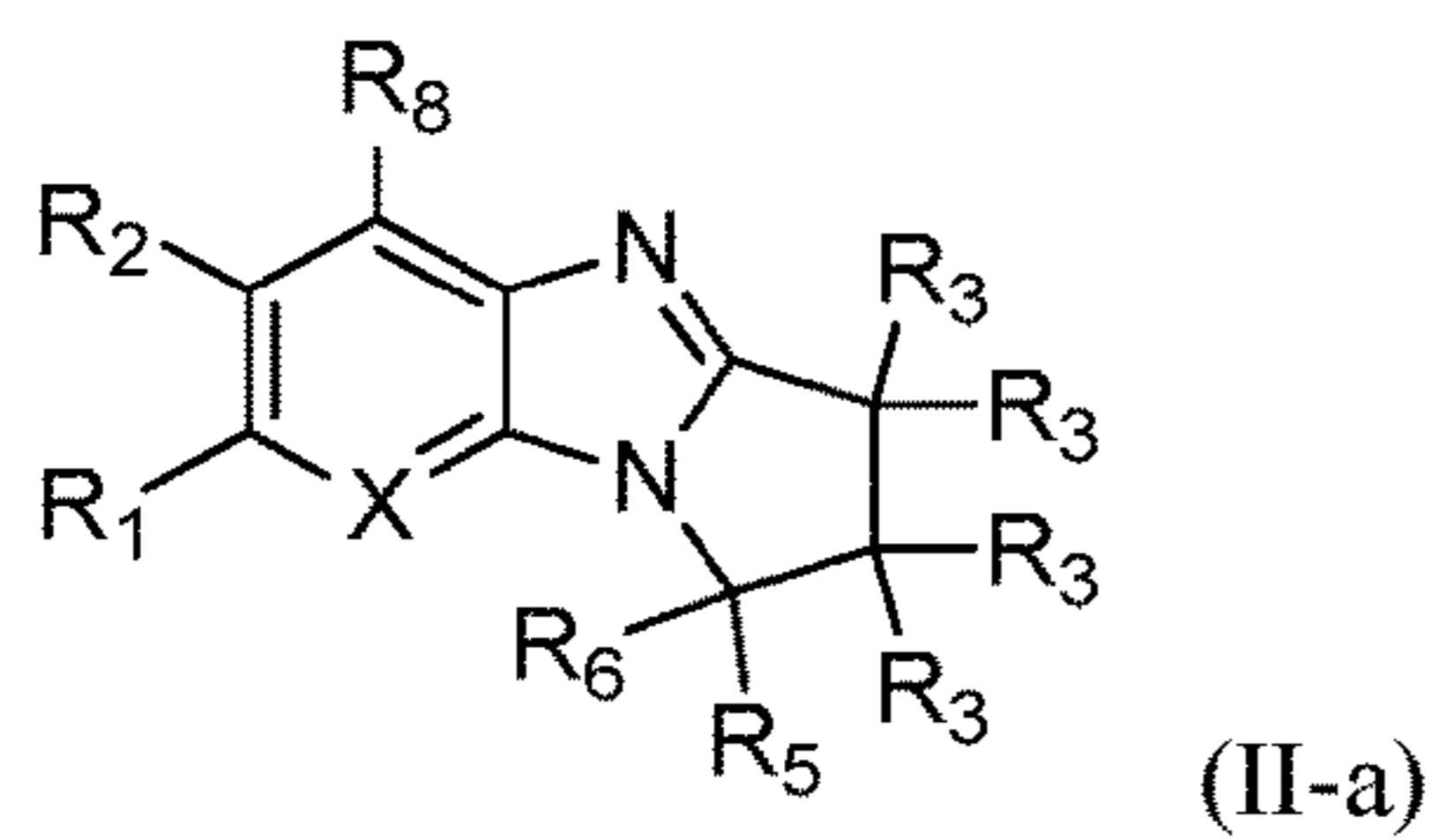
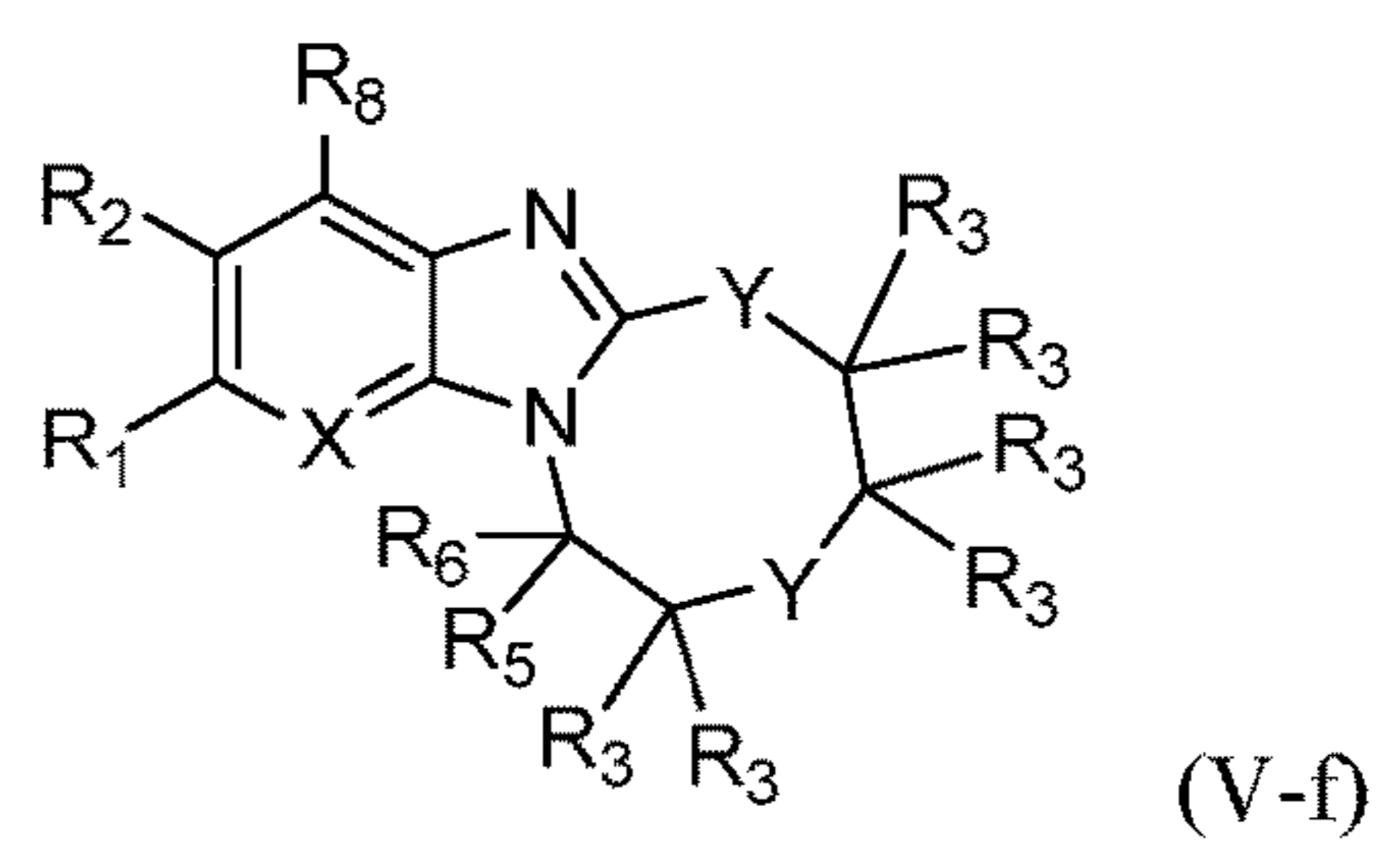
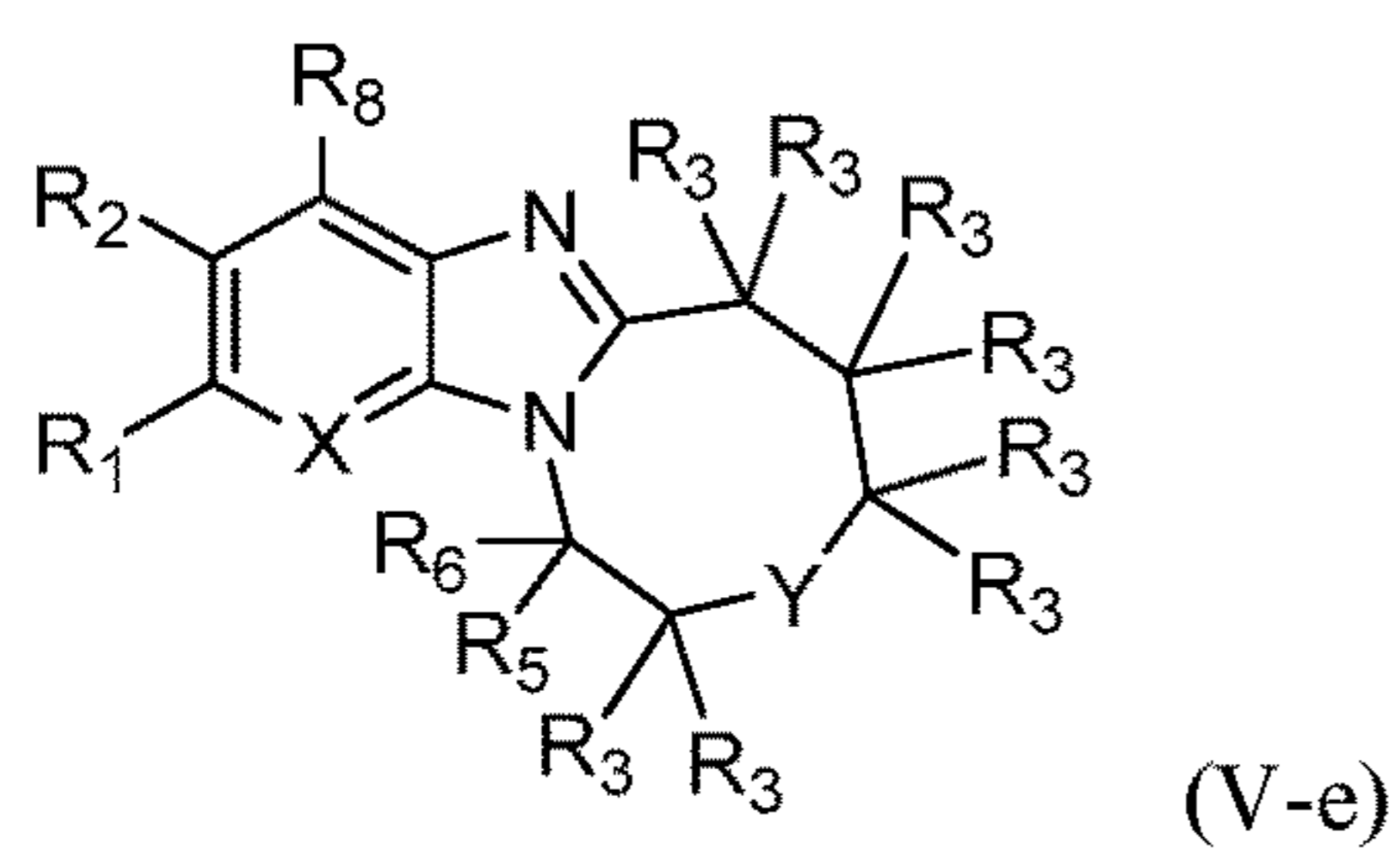
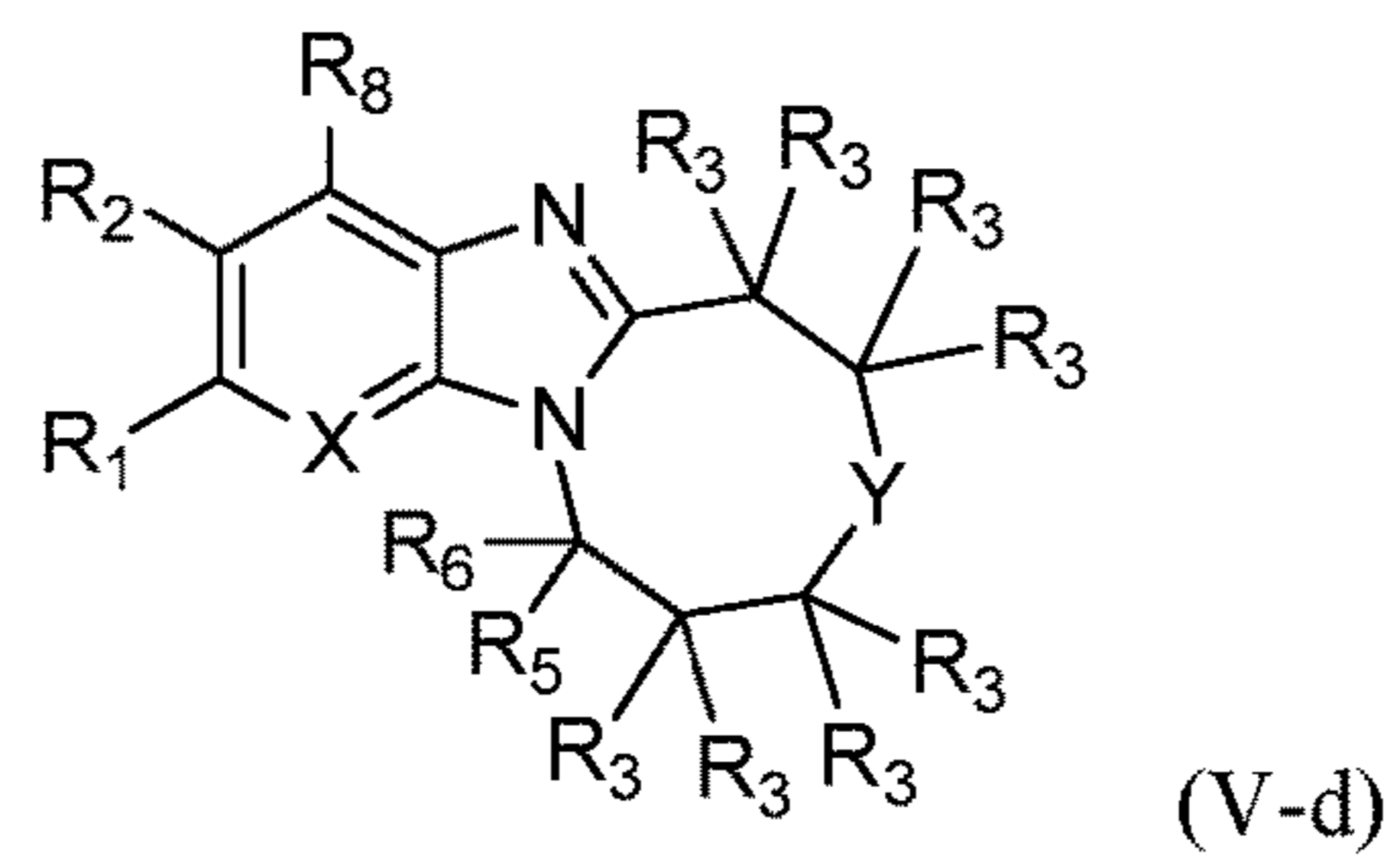
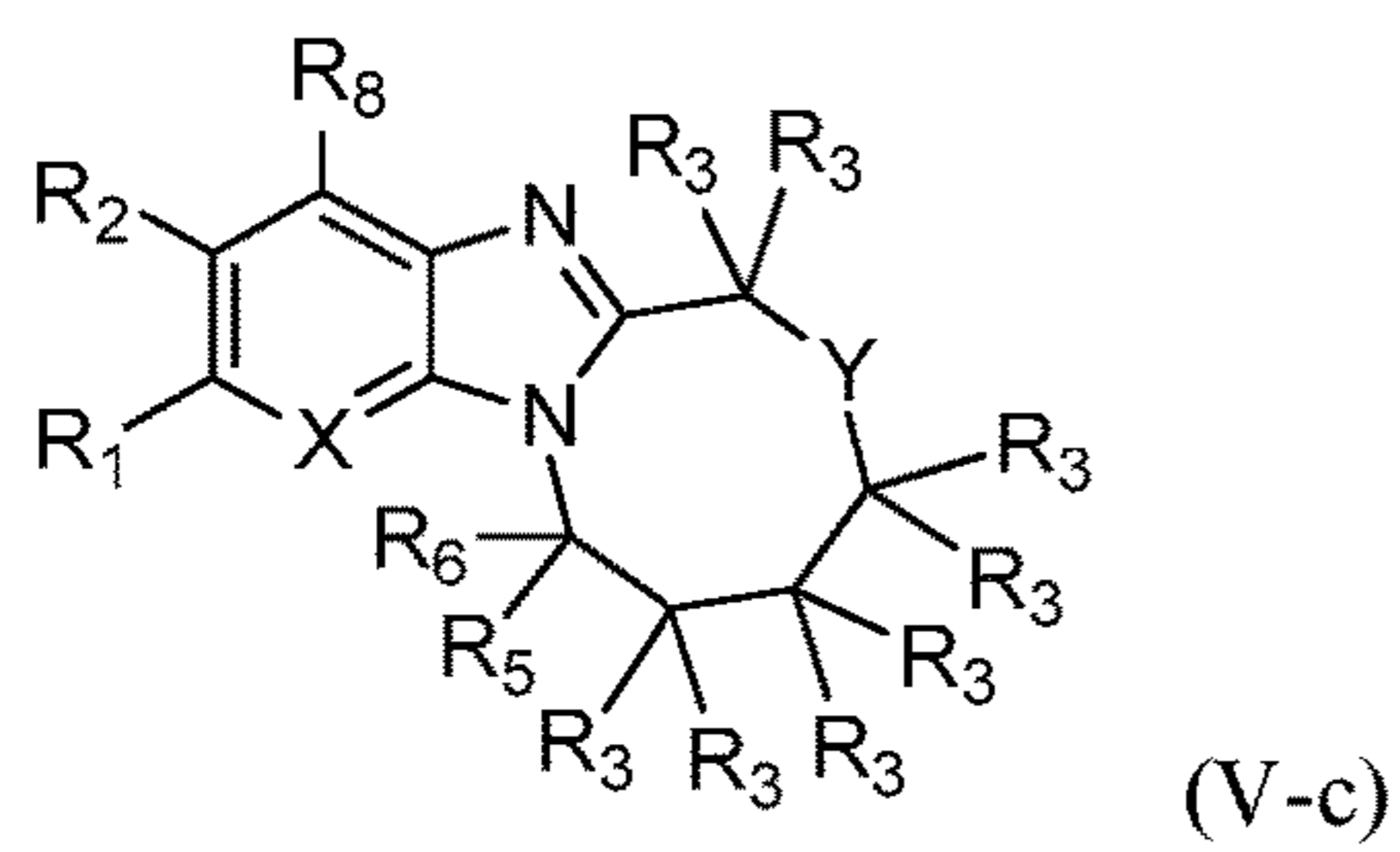
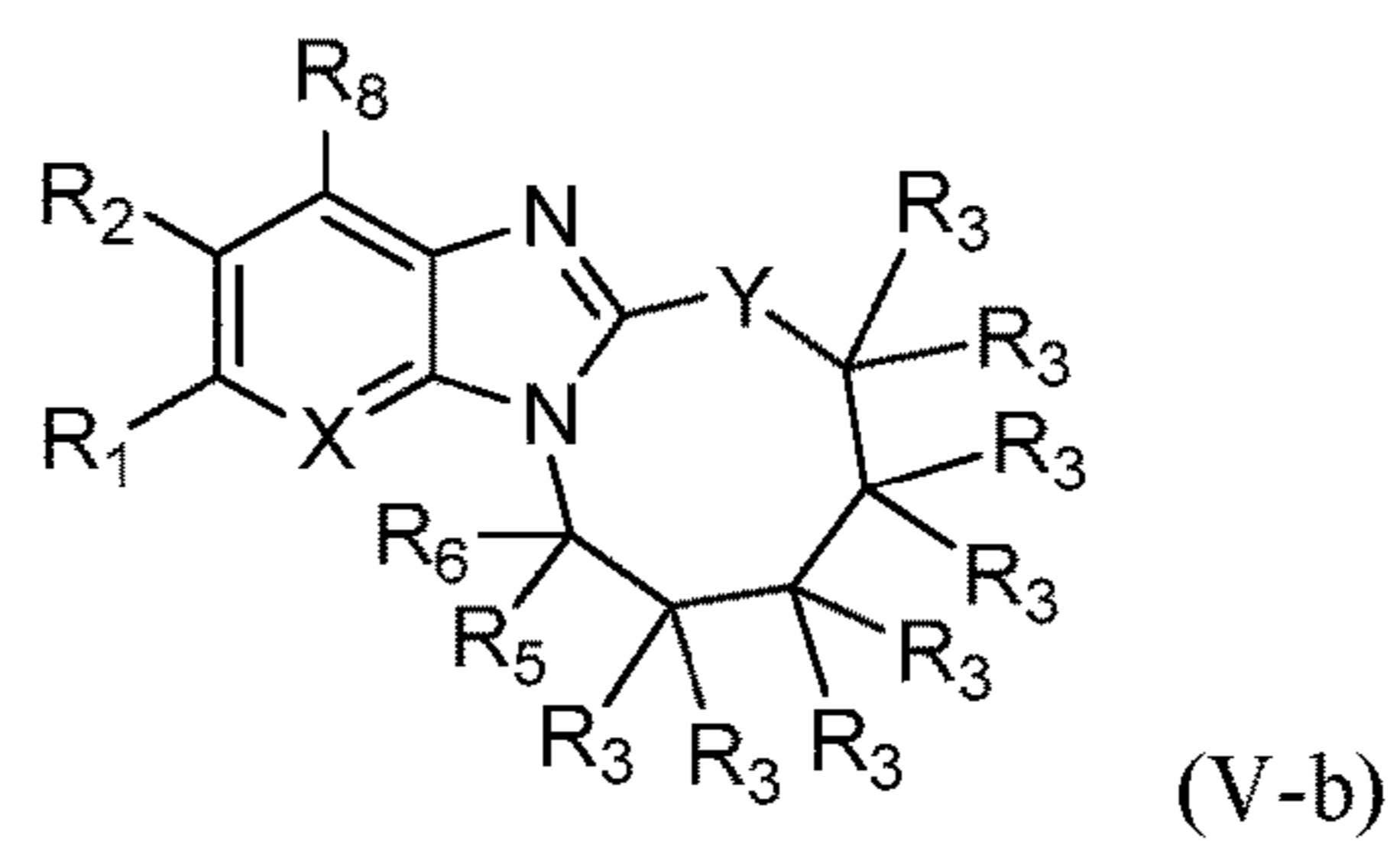
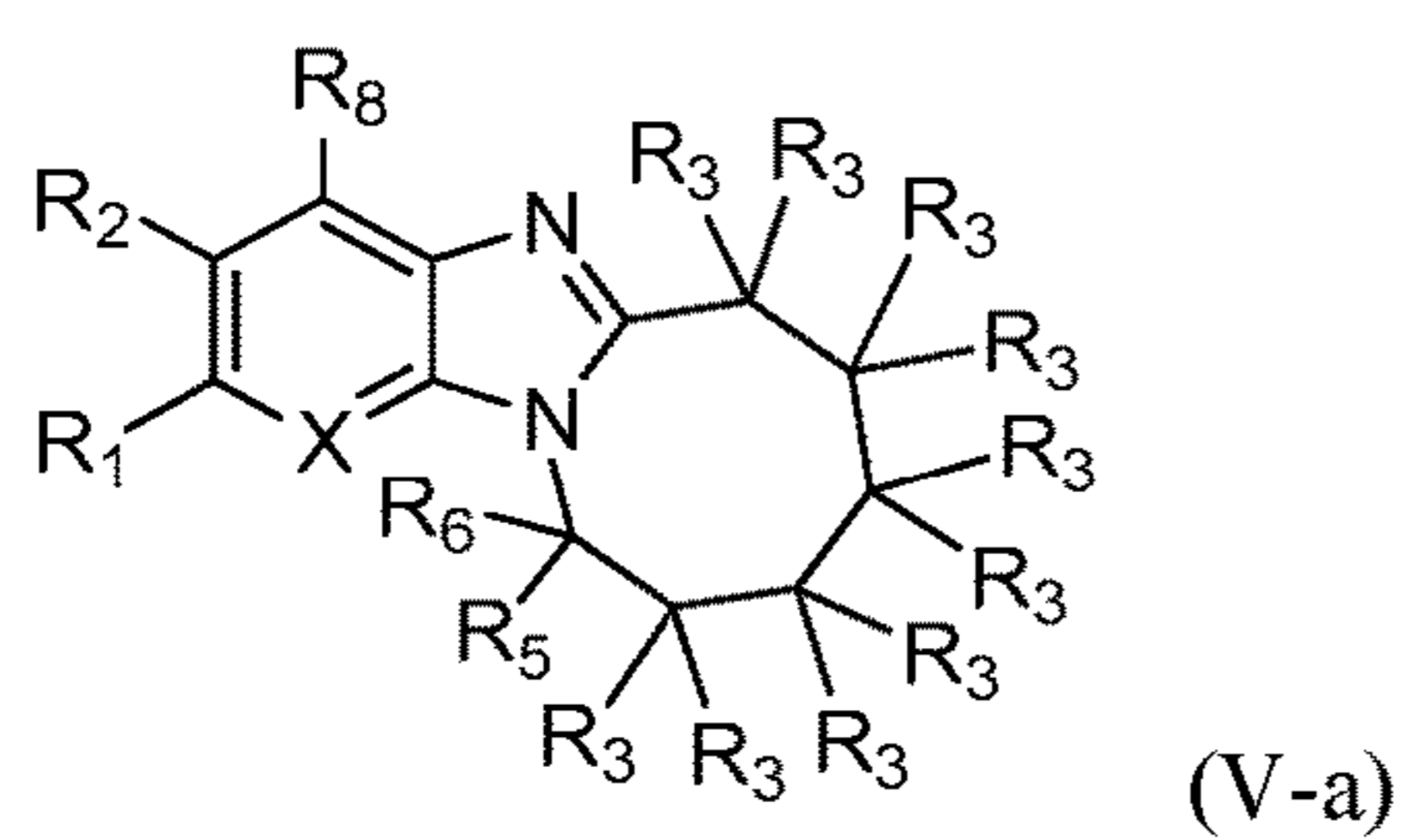




FIG. 3



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**SUBSTITUTED TRICYCLIC  
HETEROCYCLIC COMPOUNDS****CROSS-REFERENCE TO RELATED  
APPLICATIONS**

This application is a national phase application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2016/022737, filed Mar. 17, 2016, which claims priority to U.S. Application Ser. No. 62/134,769, filed Mar. 18, 2015, which are expressly incorporated fully herein by reference.

**DESCRIPTION**

The present invention generally relates to substituted tricyclic heterocyclic compounds useful as modulators of TNF $\alpha$  signaling. Provided herein are substituted tricyclic heterocyclic compounds, compositions comprising such compounds, and methods of their use. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention that are useful for the treatment of conditions related to TNF $\alpha$  activity, including inflammatory and autoimmune disorders.

TNF $\alpha$  is the first and archetypical member of the TNF superfamily (TNFSF) of ligands. TNFSF ligands are involved in the regulation of several key biological processes including cell differentiation, cell survival, cell death, and inflammation. Ligands of the TNF superfamily play a pivotal role in the regulation and orchestration of the immune and inflammatory responses at multiple levels. A common structural feature of TNFSF ligands is the formation of trimeric complexes that can bind to and activate specific TNFSF receptors. Similar to several other family members, TNF $\alpha$  is a type II transmembrane protein that can be secreted as a soluble form following proteolytic cleavage by a metalloprotease. Both the transmembrane and soluble forms of TNF $\alpha$  form biologically active trimeric complexes that signal through TNF receptors 1 and 2. TNF $\alpha$  can act on multiple cell types (T cells, monocytes, endothelial cells) through TNFRs to induce activation of the immune system, production of inflammatory cytokines, osteoclastogenesis, and cell death.

Based on their physiological and pathophysiological functions, TNF and TNFSF ligands are implicated in the pathogenesis of a number of inflammatory and autoimmune disorders (see, for example, Keystone, E. C. et al., *J. Rheumatol.*, 37:27-39 (2010); and Sedger, L. M. et al., *Cytokine Growth Factor Rev.*, 25(4):453-472 (2014)). To date, a number of TNF $\alpha$  modulating agents have been developed and are commercially available. The mechanism of action of clinically-proven protein-based therapeutic agents directed against TNF $\alpha$  is to act as competitive antagonists to inhibit TNF $\alpha$  from binding to TNFR1 and TNFR2. These agents include antibodies specific to TNF $\alpha$  including adalimumab, golimumab, certolizumab pegol, and infliximab. Another approved agent for the treatment of TNF $\alpha$ -mediated disorders is etanercept, a chimera of the immunoglobulin molecule and the TNFR2 ectodomain which also prevents TNF $\alpha$  from binding to the cellular receptors.

Being modulators of human TNF $\alpha$  activity, the substituted tricyclic heterocyclic compounds are beneficial in the treatment and/or prevention of a number of human maladies. These include inflammatory and autoimmune disorders, neurological and neurodegenerative disorders, pain and nociceptive disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological disorders.

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WO 2013/186229, WO 2014/009295, and WO 2014/009296 disclose compounds useful as modulators of TNF $\alpha$ .

In view of the numerous conditions that are contemplated to benefit by treatment involving modulation of TNF, it is immediately apparent that new compounds capable of modulating the signaling of TNF $\alpha$  and methods of using these compounds should provide substantial therapeutic benefits to a wide variety of patients.

The present invention relates to a new class of substituted tricyclic heterocyclic compounds found to be effective inhibitors of TNF $\alpha$  activity. These compounds are provided to be useful as pharmaceuticals with desirable stability, bioavailability, therapeutic index, and toxicity values that are important to their drugability.

**SUMMARY OF THE INVENTION**

The present invention provides compounds of Formula (I) that are useful as inhibitors of TNF $\alpha$ , and are useful for the treatment of inflammatory and autoimmune disorders, neurological and neurodegenerative disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological disorders; or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of Formula (I) or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for modulation of TNF $\alpha$  comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of Formula (I) or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating proliferative, metabolic, allergic, autoimmune and inflammatory diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of Formula (I) or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

One embodiment provides a method for treating inflammatory and autoimmune diseases. Particular, inflammatory and autoimmune diseases include, but are not limited to, systemic lupus erythematosus, psoriasis, Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease, Graves' disease, rheumatoid arthritis, lupus nephritis, cutaneous lupus, ankylosing spondylitis, cryopyrin-associated periodic syndromes (CAPS), TNF receptor associated periodic syndrome (TRAPS), Wegener's granulomatosis, sarcoidosis, familial Mediterranean fever (FMF), adult onset stills, systemic onset juvenile idiopathic arthritis, psoriatic arthritis, multiple sclerosis, neuropathic pain, gout, and gouty arthritis.

The present invention also provides the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of inflammatory and autoimmune diseases.



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The present invention also provides a compound of Formula (I) or a pharmaceutical composition in a kit with instructions for using the compound or composition.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

These and other features of the invention will be set forth in the expanded form as the disclosure continues.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated by reference to the accompanying drawings described below.

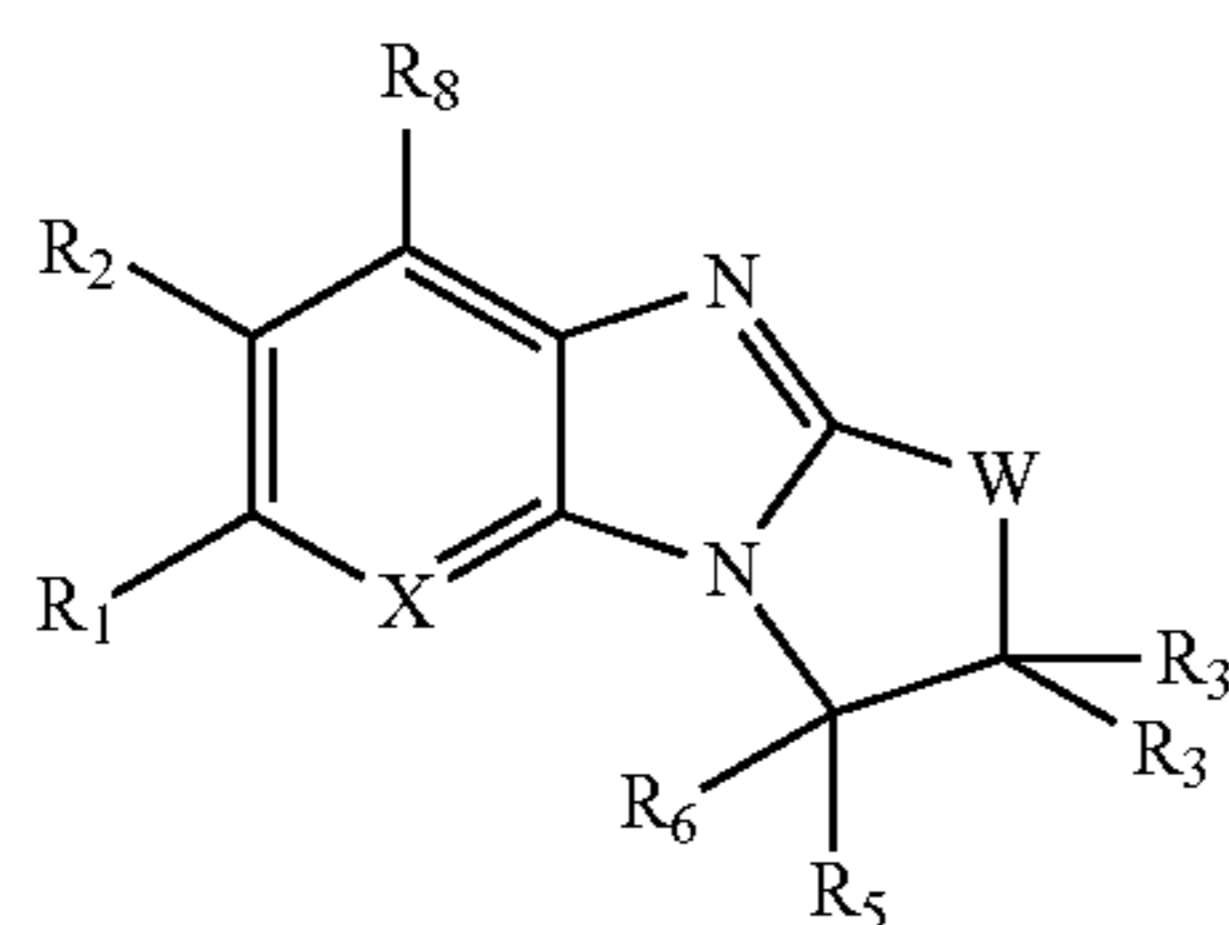
FIG. 1 shows the structures of the compounds of Formula (I), Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), Formula (I-i), Formula (I-j), and Formula (I-k).

FIG. 2 shows the structures of the compounds of Formula (II-a) and Formula (II-b); the compounds of Formula (III-a), Formula (III-b), and Formula (III-c); and the compounds of Formula (IV-a), Formula (IV-b), Formula (IV-c), and Formula (IV-d).

FIG. 3 shows the structures of the compounds of Formula (V-a), Formula (V-b), Formula (V-c), Formula (V-d), Formula (V-e), and Formula (V-f).

## DETAILED DESCRIPTION

The first aspect of the present invention provides at least one compound of Formula (I):



or a salt thereof, wherein:

X is N;

W is:

(i)  $-(CR_3R_3)_{1-4}-$ ;

(ii)  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; or

(iii)  $-Y-(CR_3R_3)_2-Y-$ ;

each Y is independently O,  $NR_4$ , or  $S(O)_p$ ;

x is zero, 1, 2, or 3;

y is zero, 1, 2, or 3, provided that (x+y) is zero, 1, 2, or 3;

$R_1$  is H,  $R_{1a}$ ,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl substituted with zero to 6  $R_{1a}$ ,  $C_{2-6}$  alkynyl substituted with zero to 4  $R_{1a}$ ,  $-(CR_gR_g)_r$ (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$ (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_2$  is H, halo,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NO_2$ ,  $C_{1-6}$  alkyl substituted with zero to 6  $R_{1a}$ ,  $-(CR_gR_g)_rOR_e$ ,  $-(CR_gR_g)_rNR_cR_c$ ,  $-(CR_gR_g)_rS(O)_pR_b$ ,  $-(CR_gR_g)_r$ (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$ (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

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each  $R_3$  is independently H, halo,  $-CN$ ,  $-OH$ ,  $-OCF_3$ ,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $-(CR_gR_g)_rC(O)R_b$ ,  $-(CR_gR_g)_rC(O)OR_b$ ,  $-(CR_gR_g)_rC(O)NR_cR_c$ ,  $-(CR_gR_g)_rOR_e$ ,  $-(CR_gR_g)_rOC(O)R_b$ ,  $-(CR_gR_g)_rOC(O)NR_cR_c$ ,  $-(CR_gR_g)_rOC(O)OR_d$ ,  $-(CR_gR_g)_rNR_cR_c$ ,  $-(CR_gR_g)_rNR_bC(O)R_d$ ,  $-(CR_gR_g)_rNR_bC(O)OR_d$ ,  $-(CR_gR_g)_rNR_bC(O)NR_cR_c$ ,  $-(CR_gR_g)_rNR_bS(O)_pR_d$ ,  $-(CR_gR_g)_rS(O)_pR_b$ ,  $-(CR_gR_g)_rS(O)_pNR_cR_c$ ,  $-(CR_gR_g)_r$ (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$ (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ); or two  $R_3$  along with the carbon atom to which they are attached form  $C=O$ ,  $C=NOR_b$ , a spirocarbocyclyl ring, or a spiroheterocyclyl ring;

each  $R_4$  is independently H,  $C_{1-6}$  alkyl substituted with zero to 6  $R_{1a}$ ,  $C_{3-7}$  cycloalkyl substituted with zero to 6  $R_{1a}$ ,  $-C(O)R_b$ ,  $-C(O)NR_cR_c$ ,  $-C(O)OR_b$ ,  $-S(O)_2R_b$ ,  $-S(O)_2NR_cR_c$ ,  $-S(O)_2OR_b$ ,  $-(CR_gR_g)_r$ (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$ (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_5$  is  $-(CR_gR_g)_r$ (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$ (5-10 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$ (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_6$  is H,  $C_{1-6}$  alkyl, or  $C_{1-6}$  haloalkyl;

or  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring, each substituted with zero to 6  $R_{5a}$ ;

each  $R_{5a}$  is independently selected from H, halo,  $-CN$ ,  $-OH$ ,  $C_{1-3}$  alkyl,  $C_{1-3}$  fluoroalkyl, or  $C_{1-3}$  alkoxy; or two  $R_{5a}$  attached to neighboring carbon atoms of the spirocarbocyclic or the spiroheterocyclic ring, form a benzo ring along with the carbon atoms to which they are attached, said benzo substituted with zero to 4  $R_j$ ; or two  $R_{5a}$  attached to the same carbon atom of the spirocarbocyclic ring or spiroheterocyclic ring, form  $=O$ ;

$R_8$  is H, halo,  $-CN$ ,  $C_{1-6}$  haloalkyl, or  $C_{1-3}$  alkoxy;

each  $R_{1a}$  is independently F, Cl,  $-CN$ ,  $C_{1-6}$  alkyl substituted with zero to 6  $R_a$ ,  $C_{3-6}$  cycloalkyl substituted with zero to 6  $R_a$ ,  $C_{1-3}$  alkoxy substituted with zero to 6  $R_a$ ,  $C_{1-3}$  haloalkoxy, heterocycloalkyl substituted with zero to 6  $R_a$ , aryl substituted with zero to 6  $R_a$ , mono- or bicyclic heteroaryl substituted with zero to 6  $R_a$ ,  $-C(O)R_b$ ,  $-C(O)OR_b$ ,  $-C(O)NR_cR_c$ ,  $-OC(O)R_b$ ,  $-OC(O)NR_cR_c$ ,  $-OC(O)OR_d$ ,  $-NR_cR_c$ ,  $-NR_bC(O)R_d$ ,  $-NR_bC(O)OR_d$ ,  $-NR_bS(O)_pR_d$ ,  $-NR_bC(O)NR_cR_c$ ,  $-NR_bS(O)_pNR_cR_c$ ,  $-S(O)_pR_b$ ,  $-S(O)_pNR_cR_c$ , or  $-C(O)NR_b(CH_2)_{1-3}NR_cR_c$ ;

each  $R_a$  is independently halo,  $-CN$ ,  $-OH$ ,  $-NO_2$ ,  $-NH_2$ ,  $C_{1-3}$  alkyl,  $C_{1-3}$  fluoroalkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl,  $C_{1-3}$  alkoxy,  $C_{1-3}$  fluoroalkoxy,  $-C(O)OH$ ,  $-C(O)(C_{1-3}$  alkyl),  $-C(O)O(C_{1-4}$  alkyl),  $-OC(O)(C_{1-3}$  alkyl),  $-NH(C_{1-3}$  alkyl),  $-N(C_{1-3}$  alkyl)<sub>2</sub>,  $-C(O)NH(C_{1-3}$  alkyl),  $-OC(O)NH(C_{1-3}$  alkyl),  $-NHC(O)NH(C_{1-3}$  alkyl),  $-C(=NH)(NH_2)$ ,  $C_{3-7}$  carbocyclyl, aryl, 5-7 membered heterocyclyl, mono- or bicyclic heteroaryl,  $-O$ (aryl),  $-O$ (benzyl),  $-O$ (heterocyclyl),  $-S(C_{1-3}$  alkyl),  $-S$ (aryl),  $-S$ (heterocyclyl),  $-S(O)$ (aryl),  $-S(O)$ (heterocyclyl),  $-S(O)_2$ (aryl),  $-S(O)_2$ (heterocyclyl),  $-NHS(O)_2$ (aryl),  $-NHS(O)_2$ (heterocyclyl),



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—NHS(O)<sub>2</sub>NH(aryl), —NHS(O)<sub>2</sub>NH(heterocyclyl),  
 —NH(aryl) —NH(heterocyclyl), —NHC(O)(aryl),  
 —NHC(O)(C<sub>1-3</sub> alkyl), —NHC(O)(heterocyclyl), —OC  
 (O)(aryl), —OC(O)(heterocyclyl), —NHC(O)NH(aryl),  
 —NHC(O)NH(heterocyclyl), —OC(O)O(C<sub>1-3</sub> alkyl),  
 —OC(O)O(aryl), —OC(O)O(heterocyclyl), —OC(O)NH  
 (aryl), —OC(O)NH(heterocyclyl), —NHC(O)O(aryl),  
 —NHC(O)O(heterocyclyl), —NHC(O)O(C<sub>1-3</sub> alkyl),  
 —C(O)NH(aryl), —C(O)NH(heterocyclyl), —C(O)O  
 (aryl), —C(O)O(heterocyclyl), —N(C<sub>1-3</sub> alkyl)S(O)<sub>2</sub>  
 (aryl), —N(C<sub>1-3</sub> alkyl)S(O)<sub>2</sub>(heterocyclyl), —N(C<sub>1-3</sub>  
 alkyl)S(O)<sub>2</sub>NH(aryl), —N(C<sub>1-3</sub> alkyl)S(O)<sub>2</sub>NH(heterocy-  
 cyclyl), —N(C<sub>1-3</sub> alkyl)(aryl), —N(C<sub>1-3</sub> alkyl)(heterocy-  
 cyclyl), —N(C<sub>1-3</sub> alkyl)C(O)(aryl), —N(C<sub>1-3</sub> alkyl)C(O)  
 (heterocyclyl), —N(C<sub>1-3</sub> alkyl)C(O)NH(aryl), —(CH<sub>2</sub>)<sub>0-3</sub>  
 C(O)NH(heterocyclyl), —OC(O)N(C<sub>1-3</sub> alkyl)(aryl),  
 —OC(O)N(C<sub>1-3</sub> alkyl)(heterocyclyl), —N(C<sub>1-3</sub> alkyl)C  
 (O)O(aryl), —N(C<sub>1-3</sub> alkyl)C(O)O(heterocyclyl), —C(O)  
 N(C<sub>1-3</sub> alkyl)(aryl), —C(O)N(C<sub>1-3</sub> alkyl)(heterocyclyl),  
 —NHS(O)<sub>2</sub>N(C<sub>1-3</sub> alkyl)(aryl), —NHS(O)<sub>2</sub>N(C<sub>1-3</sub> alkyl)  
 (heterocyclyl), —NHP(O)<sub>2</sub>N(C<sub>1-3</sub> alkyl)(aryl), —NHC  
 (O)N(C<sub>1-3</sub> alkyl)(aryl), —NHC(O)N(C<sub>1-3</sub> alkyl)(hetero-  
 cyclyl), —N(C<sub>1-3</sub> alkyl)S(O)<sub>2</sub>N(C<sub>1-3</sub> alkyl)(aryl),  
 —N(C<sub>1-3</sub> alkyl)S(O)<sub>2</sub>N(C<sub>1-3</sub> alkyl)(heterocyclyl),  
 —N(C<sub>1-3</sub> alkyl)C(O)N(C<sub>1-3</sub> alkyl)(aryl), —N(C<sub>1-3</sub> alkyl)  
 C(O)N(C<sub>1-3</sub> alkyl)(heterocyclyl), or —Si(C<sub>1-3</sub> alkyl)<sub>3</sub>;

each R<sub>b</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero  
 to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>,  
 heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl sub-  
 stituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl  
 substituted with zero to 3 R<sub>f</sub>;

each R<sub>c</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero  
 to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>,  
 heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl sub-  
 stituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl  
 substituted with zero to 3 R<sub>f</sub>; or when attached to the same  
 nitrogen, two R<sub>c</sub> along with the nitrogen atom to which  
 they are attached form 4-8 membered heterocyclic ring  
 optionally substituted with R<sub>g</sub>;

each R<sub>d</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero  
 to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>,  
 heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl sub-  
 stituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl  
 substituted with zero to 3 R<sub>f</sub>;

each R<sub>e</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero  
 to 6 R<sub>f</sub>, C<sub>1-3</sub> haloalkyl, C<sub>3-7</sub> cycloalkyl substituted with  
 zero to 6 R<sub>f</sub>, heterocycloalkyl substituted with zero to 6  
 R<sub>f</sub>, aryl substituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic  
 heteroaryl substituted with zero to 3 R<sub>f</sub>;

each R<sub>f</sub> is independently H, halo, —OH, —CN, C<sub>1-6</sub> alkyl  
 substituted with zero to 6 R<sub>a</sub>, C<sub>1-3</sub> alkoxy, C<sub>3-7</sub> cycloalkyl  
 substituted with zero to 6 R<sub>a</sub>, heterocycloalkyl substituted  
 with zero to 6 R<sub>a</sub>, aryl substituted with zero to 3 R<sub>a</sub>, or  
 mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>a</sub>;

each R<sub>g</sub> is independently H, F, —OH, —CN, C<sub>1-3</sub> alkyl,  
 —CF<sub>3</sub>, or phenyl;

each p is independently zero, 1, or 2; and

each r is independently zero, 1, 2, 3, or 4.

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —CR<sub>3</sub>R<sub>3</sub>—; and X, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>,  
 R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Compounds of  
 this embodiment have the structure of compounds of For-  
 mula (II-a).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is Y; and X, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and  
 R<sub>8</sub> are defined in the first aspect. Compounds of this embodi-  
 ment have the structure of compounds of Formula (II-b).

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One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—; and X, R<sub>1</sub>, R<sub>2</sub>,  
 R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Compounds  
 of this embodiment have the structure of compounds of  
 Formula (III-a).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —Y—(CR<sub>3</sub>R<sub>3</sub>)—; and X, Y, R<sub>1</sub>,  
 R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (III-b).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)—Y—; and X, Y, R<sub>1</sub>,  
 R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (III-c).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>3</sub>—; and X, R<sub>1</sub>, R<sub>2</sub>,  
 R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Compounds  
 of this embodiment have the structure of compounds of  
 Formula (IV-a).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—; and X, Y,  
 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (IV-b).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —CR<sub>3</sub>R<sub>3</sub>—Y—CR<sub>3</sub>R<sub>3</sub>—; and  
 X, Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first  
 aspect. Compounds of this embodiment have the structure of  
 compounds of Formula (IV-c).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—; and X, Y,  
 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (IV-d).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>4</sub>—; and X, R<sub>1</sub>, R<sub>2</sub>,  
 R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Compounds  
 of this embodiment have the structure of compounds of  
 Formula (V-a).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>3</sub>—; and X, Y,  
 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (V-b).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —CR<sub>3</sub>R<sub>3</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—;  
 and X, Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first  
 aspect. Compounds of this embodiment have the structure of  
 compounds of Formula (V-c).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—CR<sub>3</sub>R<sub>3</sub>—;  
 and X, Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first  
 aspect. Compounds of this embodiment have the structure of  
 compounds of Formula (V-d).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>3</sub>—Y—; and X, Y,  
 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (V-e).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—; and X,  
 Y, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.  
 Compounds of this embodiment have the structure of com-  
 pounds of Formula (V-f).

One embodiment provides a compound of Formula (I) or  
 a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>1-4</sub>—; and X, R<sub>1</sub>, R<sub>2</sub>,



$R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Compounds of this embodiment have the structures of Formula (II-a), Formula (III-a), Formula (IV-a), and Formula (V-a).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; and X, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ,  $R_8$ , x, and y are defined in the first aspect. Compounds of this embodiment have the structures of Formula (II-b), Formula (III-b), Formula (III-c), Formula (IV-b), Formula (IV-c), Formula (IV-d), Formula (V-b), Formula (V-c), Formula (V-d), and Formula (V-e).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-CR_3R_3-$  or  $-Y-$ ; and X, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are the compounds of Formula (II-a) and Formula (II-b).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_2-$ ,  $-Y-CR_3R_3-$ , or  $-CR_3R_3-Y-$ ; and X, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are the compounds of Formula (III-a), Formula (III-b), and Formula (III-c).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_3-$ ,  $-Y-(CR_3R_3)_2-$ ,  $-CR_3R_3-Y-CR_3R_3-$ , or  $-(CR_3R_3)_2-Y-$ ; and X, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are the compounds of Formula (IV-a), Formula (IV-b), Formula (IV-c), and Formula (IV-d).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_4-$ ,  $-Y-(CR_3R_3)_3-$ ,  $-CR_3R_3-Y-(CR_3R_3)_2-$ ,  $-(CR_3R_3)_2-Y-CR_3R_3-$ ,  $-(CR_3R_3)_3-Y-$ , or  $-Y-(CR_3R_3)_2-Y-$ ; and X, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are the compounds of Formula (V-a), Formula (V-b), Formula (V-c), Formula (V-d), Formula (V-e), or Formula (V-f).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; Y is O; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ,  $R_8$ , x, and y are defined in the first aspect. Compounds of this embodiment have the structures of Formula (II-b), Formula (III-b), Formula (III-c), Formula (IV-b), Formula (IV-c), Formula (IV-d), Formula (V-b), Formula (V-c), Formula (V-d), and Formula (V-e).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; Y is  $NR_4$ ; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_8$ , x, and y are defined in the first aspect. Compounds of this embodiment have the structures of Formula (II-b), Formula (III-b), Formula (III-c), Formula (IV-b), Formula (IV-c), Formula (IV-d), Formula (V-b), Formula (V-c), Formula (V-d), and Formula (V-e).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; Y is  $S(O)_p$ ; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ,  $R_8$ , p, x, and y are defined in the first aspect. Compounds of this embodiment have the structures of Formula (II-b), Formula (III-b), Formula (III-c), Formula (IV-b), Formula (IV-c), Formula (IV-d), Formula (V-b), Formula (V-c), Formula (V-d), and Formula (V-e). Included in this embodiment are compounds in which Y is  $S(O)_2$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-Y-(CR_3R_3)_2-Y-$ ; each Y is O; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Compounds of this embodiment have the structure of Formula (IV-f).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-Y-(CR_3R_3)_2-Y-$ ; each Y is  $NR_4$ ; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Compounds of this embodiment have the structure of Formula (IV-f).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-Y-(CR_3R_3)_2-Y-$ ; each Y is independently O or  $NR_4$ ; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Compounds of this embodiment have the structure of Formula (IV-f).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is  $-Y-(CR_3R_3)_2-Y-$ ; each Y is independently  $S(O)_p$ ; and X,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Compounds of this embodiment have the structure of Formula (IV-f).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is H,  $R_{1a}$ ,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl substituted with zero to 6  $R_{1a}$ , or  $C_{2-6}$  alkynyl substituted with zero to 4  $R_{1a}$ ; and X, W,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is  $R_{1a}$ ; and X, W,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is: F, Cl, Br, or  $-CN$ ; and X, W,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl substituted with zero to 6  $R_{1a}$ , or  $C_{2-6}$  alkynyl substituted with zero to 4  $R_{1a}$ ; and X, W,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ); and X, W,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ,  $R_8$ ,  $R_g$ , and r are defined in the first aspect. Included in this embodiment are compounds in which r is 1. Also included in this embodiment are compounds in which  $R_1$  is  $-CH_2$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-CH_2$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-CH_2$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-CH_2$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is 3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ , aryl substituted with zero to 3  $R_{1a}$ , 5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ , or mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ; and X, W,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_1$  is aryl substituted with zero to 3  $R_{1a}$  or mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_1$  is pyrazolyl, isoxazolyl, phenyl, pyridinyl, pyridinonyl, pyridazinyl, pyrimidinyl, indolyl, isoindolinonyl, benzoimidazolyl, or benzothiazolyl, each substituted with zero to 3 substituents independently selected from F, Cl,  $-CN$ ,  $C_{1-3}$  alkyl,  $-CHF_2$ ,  $-CF_3$ ,  $C_{1-3}$  cyanoalkyl,  $C_{1-3}$  hydroxyalkyl,  $-CH_2NH_2$ ,  $-CH_2C(O)OH$ ,  $-CH=CHCH_3$ ,  $-OCH_3$ ,  $-C(O)NH_2$ ,  $-C(O)NH(C_{1-3}$  alkyl),  $-C(O)N(CH_3)(C_{1-3}$  alkyl),  $-C(O)NH(C_{1-3}$  cyanoalkyl),  $-C(O)NH(C_{1-3}$  hydroxyalkyl),  $-C(O)NHCH_2CH_2CH_2N(CH_3)_2$ ,  $-C(O)NHCH_2CH_2$  (morpholinyl),  $-S(O)_2(C_{1-3}$  alkyl),  $-S(O)_2NH_2$ ,  $-S(O)_2NH(C_{1-2}$  alkyl),  $-S(O)_2NH(C_{3-6}$  cycloalkyl),  $-NH(C_{1-3}$  alkyl),



—N(C<sub>1-3</sub> alkyl)<sub>2</sub>, —NHS(O)<sub>2</sub>(C<sub>1-3</sub> alkyl), —C(O)NH((C<sub>3-6</sub> cycloalkyl), —C(O)(azetidyl), C<sub>3-6</sub> cycloalkyl, cyanocyclopropyl, piperidinyl, piperazinyl, phenyl, methyloxadiazolyl, amino-oxadiazolyl, and methylamino thiadiazolyl; and X, W, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein R<sub>1</sub> is: (i) F, Cl, Br, —CN; or (ii) pyrazolyl, isoxazolyl, phenyl, pyridinyl, pyridinonyl, pyridazinyl, pyrimidinyl, indolyl, isoindolinonyl, benzoimidazolyl, or benzothiazolyl, each substituted with zero to 3 substituents independently selected from F, Cl, —CN, C<sub>1-3</sub> alkyl, —CHF<sub>2</sub>, —CF<sub>3</sub>, C<sub>1-3</sub> cyanoalkyl, C<sub>1-3</sub> hydroxyalkyl, —CH<sub>2</sub>NH<sub>2</sub>, —CH<sub>2</sub>C(O)OH, —CH=CHCH<sub>3</sub>, —OCH<sub>3</sub>, —C(O)NH<sub>2</sub>, —C(O)NH(C<sub>1-3</sub> alkyl), —C(O)N(CH<sub>3</sub>)(C<sub>1-3</sub> alkyl), —C(O)NH(C<sub>1-3</sub> cyanoalkyl), —C(O)NH(C<sub>1-3</sub> hydroxyalkyl), —C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, —C(O)NHCH<sub>2</sub>CH<sub>2</sub>(morpholinyl), —S(O)<sub>2</sub>(C<sub>1-3</sub> alkyl), —S(O)<sub>2</sub>NH<sub>2</sub>, —S(O)<sub>2</sub>NH(C<sub>1-2</sub> alkyl), —S(O)<sub>2</sub>NH(C<sub>3-6</sub> cycloalkyl), —NH(C<sub>1-3</sub> alkyl), —N(C<sub>1-3</sub> alkyl)<sub>2</sub>, —NHS(O)<sub>2</sub>(C<sub>1-3</sub> alkyl), —C(O)NH((C<sub>3-6</sub> cycloalkyl), —C(O)(azetidyl), C<sub>3-6</sub> cycloalkyl, cyanocyclopropyl, piperazinyl, phenyl, methyloxadiazolyl, amino-oxadiazolyl, and methylamino thiadiazolyl; phenyl, piperazinyl, and piperidinyl; and X, W, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein R<sub>2</sub> is H, halo, —CN, —CF<sub>3</sub>, —OCF<sub>3</sub>, —NO<sub>2</sub>, or C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>1a</sub>; and X, W, R<sub>1a</sub>, R<sub>1</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Included in this embodiment are compounds in which R<sub>2</sub> is H, halo, —CN, —CF<sub>3</sub>, or —OCF<sub>3</sub>. Also included in this embodiment are compounds in which R<sub>2</sub> is H or F.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein R<sub>2</sub> is —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OR<sub>e</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>S(O)<sub>p</sub>R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(aryl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(monocyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>); and X, W, R<sub>1</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>1a</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>e</sub>, R<sub>g</sub>, p, and r are defined in the first aspect. Included in this embodiment are compounds in which r is 1. Also included in this embodiment are compounds in which R<sub>1</sub> is —CH<sub>2</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —CH<sub>2</sub>(aryl substituted with zero to 3 R<sub>1a</sub>), —CH<sub>2</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —CH<sub>2</sub>(mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein R<sub>2</sub> is H, halo, —CN, —CF<sub>3</sub>, or —OCF<sub>3</sub>; and X, W, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Included in this embodiment are compounds in which R<sub>2</sub> is H or halo. Also included are compounds in which R<sub>2</sub> is H or F.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein each R<sub>3</sub> is independently H, halo, —CN, —OH, —OCF<sub>3</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)R<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)OR<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OR<sub>e</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)R<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)OR<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)OR<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>S(O)<sub>p</sub>R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>S(O)<sub>p</sub>R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>S(O)<sub>p</sub>NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(aryl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(mono- or

bicyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>); and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>1a</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub>, R<sub>g</sub>, p, and r are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein each R<sub>3</sub> is independently H, halo, —CN, —OH, —OCF<sub>3</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>2-6</sub> alkenyl, or C<sub>2-6</sub> alkynyl; and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Included in this embodiment are compounds in which R<sub>3</sub> is H, —OH, —CN, —OCF<sub>3</sub>, C<sub>1-3</sub> alkyl, or C<sub>1-3</sub> fluoroalkyl. Also included in this embodiment are compounds in which R<sub>3</sub> is H, —OH, —CN, —OCF<sub>3</sub>, —CH<sub>3</sub>, and —CF<sub>3</sub>.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein each R<sub>3</sub> is independently H, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)R<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)OR<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>C(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OR<sub>e</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)R<sub>b</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>OC(O)OR<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)OR<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>C(O)NR<sub>c</sub>R<sub>c</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>NR<sub>b</sub>S(O)<sub>p</sub>R<sub>d</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>S(O)<sub>p</sub>R<sub>d</sub>, or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>S(O)<sub>p</sub>NR<sub>c</sub>R<sub>c</sub>; and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub>, R<sub>g</sub>, p, and r are defined in the first aspect. Included in this embodiment are compounds in which each R<sub>g</sub> is H.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein each R<sub>3</sub> is independently H, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(aryl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>); and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>1a</sub>, R<sub>g</sub>, and r are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein two R<sub>3</sub> along with the carbon atom to which they are attached form C=O, C=NOR<sub>b</sub>, a spirocarbocyclyl ring, or a spiroheterocyclyl ring; the remaining R<sub>3</sub> are H, —OH, or —CH<sub>3</sub>; and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, and R<sub>b</sub> are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein each R<sub>3</sub> is independently H, —OH, or —CH<sub>3</sub>; and X, W, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>8</sub> are defined in the first aspect. Included in this embodiment are compounds in which R<sub>3</sub> is H or —OH.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>x</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>y</sub>— or —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—; each Y is independently O, NR<sub>4</sub>, or S(O)<sub>p</sub>, provided that at least one Y is NR<sub>4</sub>; each R<sub>4</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>1a</sub>, or C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>1a</sub>; and X, R<sub>1</sub>, R<sub>1a</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, p, x, and y are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>x</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>y</sub>— or —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—; each Y is independently O, NR<sub>4</sub>, or S(O)<sub>p</sub>, provided that at least one Y is NR<sub>4</sub>; each R<sub>4</sub> is independently —C(O)R<sub>b</sub>, —C(O)NR<sub>c</sub>R<sub>c</sub>, —C(O)OR<sub>b</sub>, —S(O)<sub>2</sub>R<sub>b</sub>, —S(O)<sub>2</sub>NR<sub>c</sub>R<sub>c</sub>, or —S(O)<sub>2</sub>OR<sub>b</sub>; and X, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>8</sub>, R<sub>b</sub>, R<sub>c</sub>, p, x, and y are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>x</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>y</sub>— or —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—; each Y is independently O, NR<sub>4</sub>, or S(O)<sub>p</sub>, provided that at least one Y is NR<sub>4</sub>; each R<sub>4</sub> is independently —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(aryl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(monocyclic



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heteroaryl substituted with zero to 3  $R_{1a}$ ); and X,  $R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ,  $R_8$ ,  $R_b$ ,  $R_c$ ,  $R_g$ , p, r, x, and y are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  is  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ) or  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ); and X, W,  $R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_8$ ,  $R_g$ , and r are defined in the first aspect. Included in this embodiment are compounds in which  $R_5$  is  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ). Also included in this embodiment are compounds in which each  $R_g$  is H or  $-OH$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  is  $-(CR_gR_g)_r$  (phenyl substituted with zero to 3  $R_{1a}$ ); and X, W,  $R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_8$ ,  $R_g$ , and r are defined in the first aspect. Included in this embodiment are compounds in which  $R_5$  is  $-(CH_2)_r$  (phenyl substituted with zero to 3  $R_{1a}$ ). Also included in this embodiment are compounds in which  $R_5$  is phenyl substituted with zero to 3  $R_{1a}$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  is  $-(CR_gR_g)_r$  (5-10 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ) or  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ); and X, W,  $R_1$ ,  $R_{1a}$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_8$ ,  $R_g$ , and r are defined in the first aspect. Included in this embodiment are compounds in which  $R_5$  is  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ ). Also included in this embodiment are compounds in which each  $R_g$  is H.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_6$  is H or  $C_{1-6}$  alkyl; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_6$  is H or  $C_{1-3}$  alkyl. Also included in this embodiment are compounds in which  $R_6$  is H or  $C_{1-2}$  alkyl.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_6$  is H or  $C_{1-6}$  haloalkyl; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_6$  is H or  $C_{1-3}$  fluoroalkyl. Also included in this embodiment are compounds in which  $R_6$  is H or  $-CF_3$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_6$  is H or  $-CH_3$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_6$  is H; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_6$  is  $-CH_3$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclic ring or spiroheterocyclic ring, each substituted with zero to 6  $R_{5a}$ ; and X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds having the structure of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), Formula (I-i), Formula (I-j), and Formula (I-k).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclic ring substituted with zero to 6  $R_{5a}$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$  and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds having the

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structure of Formula (I-a), Formula (I-b), Formula (I-d), Formula (I-f), and Formula (I-i).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclic ring substituted with zero to 6  $R_{5a}$ , in which two  $R_{5a}$  attached to neighboring carbon atoms of the spirocarbocyclic ring form a benzo ring along with the carbon atoms to which they are attached, and said benzo is substituted with zero to 4  $R_f$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$  and  $R_f$  are defined in the first aspect. Included in this embodiment are compounds having the structure of Formula (I-d) and Formula (I-i).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spiroheterocyclic ring substituted with zero to 6  $R_{5a}$ ; and X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds in which the spiroheterocyclic ring includes a heteroatom selected from oxygen or nitrogen. Also included in this embodiment are compounds in which the spiroheterocyclic ring includes an oxygen heteroatom. Included in this embodiment are compounds having the structure of Formula (I-c), Formula (I-e), Formula (I-g), Formula (I-h), Formula (I-j), and Formula (I-k).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spiroheterocyclic ring substituted with zero to 6  $R_{5a}$ , in which two  $R_{5a}$  attached to neighboring carbon atoms of the spiroheterocyclic ring form a benzo ring along with the carbon atoms to which they are attached, and said benzo is substituted with zero to 4  $R_f$ ; and X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect. Included in this embodiment are compounds in which the spiroheterocyclic ring includes a heteroatom selected from oxygen or nitrogen. Also included in this embodiment are compounds in which the spiroheterocyclic ring includes an oxygen heteroatom. Included in this embodiment are compounds having the structure of Formula (I-e), Formula (I-j), and Formula (I-k).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_8$  is H, halo, or  $-CN$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_6$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_8$  is H, F, Cl, or  $-CN$ . Also included in this embodiment are compounds in which  $R_8$  is H, F, or  $-CN$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_8$  is H,  $C_{1-6}$  haloalkyl, or  $C_{1-3}$  alkoxy; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_6$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_8$  is H,  $C_{1-3}$  haloalkyl, or  $C_{1-3}$  alkoxy. Also included in this embodiment are compounds in which  $R_8$  is  $C_{1-6}$  haloalkyl, or  $C_{1-3}$  alkoxy.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_8$  is H,  $C_{1-6}$  fluoroalkyl, or  $C_{1-3}$  alkoxy; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_6$  are defined in the first aspect. Included in this embodiment are compounds in which  $R_8$  is H,  $C_{1-3}$  fluoroalkyl, or  $C_{1-3}$  alkoxy. Also included in this embodiment are compounds in which  $R_8$  is  $C_{1-6}$  fluoroalkyl, or  $C_{1-3}$  alkoxy.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_8$  is H, F, Cl,  $-CN$ ,  $C_{1-2}$  fluoroalkyl, or  $C_{1-3}$  alkoxy; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , and  $R_6$  are defined in the first aspect. Included in this embodiment are com-



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pounds in which  $R_8$  is H, F,  $-\text{CN}$ ,  $-\text{CF}_3$ , or  $-\text{OCH}_3$ . Also included in this embodiment are compounds in which  $R_8$  is H, F, or  $-\text{CF}_3$ .

One embodiment provides a compound of Formula (I-a) or a salt thereof, wherein X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-b) or a salt thereof, wherein X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-c) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$  and  $R_8$ , are defined in the first aspect.

One embodiment provides a compound of Formula (I-d) or a salt thereof, wherein X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-e) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-f) or a salt thereof, wherein X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-g) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-h) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ , and  $R_8$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-i) or a salt thereof, wherein X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-j) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect.

One embodiment provides a compound of Formula (I-k) or a salt thereof, wherein X, W, Y,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$ ,  $R_8$ , and  $R_f$  are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclic ring substituted with zero to 6  $R_{5a}$ , in which two  $R_{5a}$  attached to the same carbon atom of the spirocarbocyclic ring or the spiroheterocyclic ring form  $=\text{O}$ ; and X, W,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_{5a}$  and  $R_8$  are defined in the first aspect. Included in this embodiment are compounds of Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), and Formula (I-g).

One embodiment provides a compound of Formula (I) or a salt thereof, wherein: W is (i)  $-(\text{CR}_3\text{R}_3)_{1-3}-$ ; or (ii)  $-(\text{CR}_3\text{R}_3)_x-\text{Y}-(\text{CR}_3\text{R}_3)_y-$ ; x is zero, 1, or 2; y is zero, 1, or 2, provided that (x+y) is zero, 1, or 2;  $R_1$  is H,  $R_{1a}$ ,  $C_{1-3}$  fluoroalkyl,  $C_{2-4}$  alkenyl substituted with zero to 4  $R_{1a}$ ,  $C_{2-4}$  alkynyl substituted with zero to 3  $R_{1a}$ ,  $-(\text{CR}_g\text{R}_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(\text{CR}_g\text{R}_g)_r$  (phenyl substituted with zero to 3  $R_{1a}$ ),  $-(\text{CR}_g\text{R}_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(\text{CR}_g\text{R}_g)_r$  (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ ); each  $R_{1a}$  is independently F, Cl,  $-\text{CN}$ ,  $C_{1-3}$  alkyl substituted with zero to 4  $R_a$ ,  $C_{3-6}$  cycloalkyl substituted with zero to 4  $R_a$ ,  $C_{1-2}$  alkoxy substituted with zero to 3  $R_a$ ,  $C_{1-2}$  fluoroalkoxy, heterocycloalkyl substituted with zero to 3  $R_a$ , phenyl substituted with zero to 3  $R_a$ , or monocyclic heteroaryl substituted with zero to 3  $R_a$ ; each  $R_a$  is independently F, Cl, Br,  $-\text{CN}$ ,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{CHF}_2$ , or  $-\text{CF}_3$ ;  $R_2$  is H, F, Cl, Br,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $C_{1-3}$  alkyl substituted with zero to 4  $R_{1a}$ , or  $C_{3-6}$  cycloalkyl substituted with zero to 4  $R_{1a}$ ; each  $R_3$  is independently H, F, Cl,  $-\text{CN}$ ,  $-\text{OH}$ ,  $-\text{OCF}_3$ ,  $C_{1-3}$  alkyl,

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$C_{1-3}$  fluoroalkyl, or  $C_{2-3}$  alkenyl;  $R_4$  is H,  $C_{1-3}$  alkyl substituted with zero to 4  $R_{1a}$ , or  $C_{3-6}$  cycloalkyl substituted with zero to 4  $R_{1a}$ ;  $R_5$  is  $-(\text{CR}_g\text{R}_g)_r$  (3-6 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(\text{CR}_g\text{R}_g)_r$  (phenyl substituted with zero to 3  $R_{1a}$ ),  $-(\text{CR}_g\text{R}_g)_r$  (5-10 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(\text{CR}_g\text{R}_g)_r$  (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ );  $R_6$  is H,  $C_{1-3}$  alkyl, or  $C_{1-3}$  fluoroalkyl;  $R_8$  is H, F, Cl, Br,  $-\text{CN}$ ,  $C_{1-3}$  fluoroalkyl, or  $C_{1-3}$  alkoxy; each r is independently zero, 1, or 2; and X, Y,  $R_g$ , and p are defined in the first aspect.

One embodiment provides a compound of Formula (I) or a salt thereof, wherein: W is  $-\text{CR}_3\text{R}_3-$ ;  $R_1$  is phenyl, pyrazolyl, pyridinyl, or pyrimidinyl, each substituted with zero to 1 substituents selected from  $-\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_2\text{OH}$ ,  $-\text{OCH}_3$ , morpholinyl, methylpiperazinyl, and carboxymethyl piperazinyl;  $R_2$  is H; each  $R_3$  is independently H, F, or  $-\text{OH}$ ;  $R_5$  is phenyl substituted with zero to 2 substituents independently selected from F,  $-\text{CH}_3$ ,  $-\text{CF}_3$ ,  $-\text{OCH}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCF}_3$ , or cyclopropyl;  $R_6$  is H;  $R_8$  is H; and X is defined in the first aspect. Included in this embodiment are compounds in which W is  $-\text{CH}_2-$ ,  $-\text{CHF}-$ , or  $-\text{CH}(\text{OH})-$ .

One embodiment provides a compound of Formula (I) or a salt thereof, wherein said compound is 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (1); 8-(2-(difluoromethoxy)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (2); 8-(2-fluoro-6-(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (3); 8-(2,5-dimethylphenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (4); 8-(2,5-dimethylphenyl)-2-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (5); 8-(2,5-dimethylphenyl)-2-(2-morpholinopyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (6); 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-methyl-5-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (7); 8-(2,5-bis(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (8); 8-(2-cyclopropylphenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (9); 8-(2-(difluoromethoxy)phenyl)-2-(2-morpholinopyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (10); 8-(2-(difluoromethoxy)phenyl)-2-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (11); 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (12); 8-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (13); 2-(4-(6-fluoro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (14); 2-(4-(8-(2-(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (15); 2-(5-(8-(2-(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (16); 4-(5-(8-(2-(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)morpholine (17); 8-(2-(difluoromethoxy)phenyl)-6-fluoro-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (18); 8-(2-(difluoromethoxy)phenyl)-6-fluoro-2-



(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (19); 2-(5-(8-(2,5-dimethylphenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (20); 2-(4-(8-(2-cyclopropylphenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (21); 2-(4-(6-fluoro-8-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (22); 2-(4-(6-fluoro-8-(2-fluoro-6-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (23); 2-(4-(6-fluoro-8-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (24); 2-(4-(8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (25); 2-(4-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (26); 2-(5-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (27); 4-(5-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)morpholine (28); 8-(2-(difluoromethoxy)phenyl)-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (29); 8-(2-(difluoromethoxy)phenyl)-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (30); 2-(4-(8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (31); 2-(4-(8-(2-fluoro-6-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (32); 2-(4-(8-(2-cyclopropylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (33); 2-(4-(8-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (34); 2-(4-(5-(8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)piperazin-1-yl)acetic acid (35); (R)-2-(5-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (36); (R)-2-(4-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (37); (R)-8-(2,5-dimethylphenyl)-2-(4-(4-methylpiperazin-1-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (38); (R)-8-(2,5-dimethylphenyl)-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (39); or (R)-8-(2,5-dimethylphenyl)-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (40).

## DEFINITIONS

The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. Embodiments identified herein as exemplary or preferred are intended to be illustrative and not limiting.

Unless specifically stated otherwise herein, references made in the singular may also include the plural. For example, “a” and “an” may refer to either one, or one or more.

As used herein, the phrase “compounds” refers to at least one compound. For example, a compound of Formula (I) includes a compound of Formula (I); and two or more compounds of Formula (I).

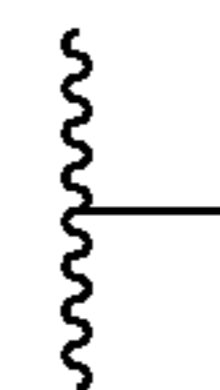
Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

Listed below are definitions of various terms used to describe the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

In accordance with a convention used in the art,



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

The terms “halo” and “halogen”, as used herein, refer to F, Cl, Br, and I.

The term “cyano” refers to the group —CN.

The term “amino” refers to the group —NH<sub>2</sub>.

The term “oxo” refers to the group =O.

The term “alkyl” as used herein, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups containing, for example, from 1 to 12 carbon atoms, from 1 to 6 carbon atoms, and from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (e.g., n-propyl and i-propyl), butyl (e.g., n-butyl, i-butyl, sec-butyl, and t-butyl), and pentyl (e.g., n-pentyl, isopentyl, neopentyl), n-hexyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, “C<sub>1-6</sub> alkyl” denotes straight and branched chain alkyl groups with one to six carbon atoms.

The term “haloalkyl” as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more halogen atoms. For example, “C<sub>1-4</sub> haloalkyl” is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> alkyl groups substituted with one or more halogen atoms. Representative examples of haloalkyl groups include, but are not limited to, —CF<sub>3</sub>, —CCl<sub>3</sub>, —CFCl<sub>2</sub>, and —CH<sub>2</sub>CF<sub>3</sub>.

The term “fluoroalkyl” as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more fluorine atoms. For example, “C<sub>1-4</sub> fluoroalkyl” is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> alkyl groups substituted with one



or more fluorine atoms. Representative examples of fluoroalkyl groups include, but are not limited to,  $-\text{CF}_3$  and  $-\text{CH}_2\text{CF}_3$ .

The term “cyanoalkyl” includes both branched and straight-chain saturated alkyl groups substituted with one or more cyano groups. For example, “cyanoalkyl” includes  $-\text{CH}_2\text{CN}$ ,  $-\text{CH}_2\text{CH}_2\text{CN}$ , and  $\text{C}_{1-4}$  cyanoalkyl.

The term “hydroxyalkyl” includes both branched and straight-chain saturated alkyl groups substituted with one or more hydroxyl groups. For example, “hydroxyalkyl” includes  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ , and  $\text{C}_{1-4}$  hydroxyalkyl.

The term “alkenyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. For example, “ $\text{C}_{2-6}$  alkenyl” denotes straight and branched chain alkenyl groups with two to six carbon atoms.

The term “alkynyl” refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Exemplary such groups include ethynyl. For example, “ $\text{C}_{2-6}$  alkynyl” denotes straight and branched chain alkynyl groups with two to six carbon atoms.

The term “cycloalkyl”, as used herein, refers to a group derived from a non-aromatic monocyclic or polycyclic hydrocarbon molecule by removal of one hydrogen atom from a saturated ring carbon atom. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms that a particular cycloalkyl group may contain. For example, “ $\text{C}_{3-6}$  cycloalkyl” denotes cycloalkyl groups with three to six carbon atoms.

The term “cycloalkenyl”, as used herein, refers to a nonaromatic cyclic hydrocarbon ring having one double bond. For example,  $\text{C}_{5-6}$  cycloalkenyl denotes cyclopentenyl and cyclohexenyl.

The term “cycloalkynyl”, as used herein, refers to a nonaromatic cyclic hydrocarbon ring having one triple bond. For example,  $\text{C}_{5-6}$  cycloalkynyl denotes cyclopentynyl and cyclohexynyl.

The term “alkoxy”, as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom, for example, methoxy group ( $-\text{OCH}_3$ ). For example, “ $\text{C}_{1-3}$  alkoxy” denotes alkoxy groups with one to three carbon atoms.

The terms “haloalkoxy” and “ $-\text{O}(\text{haloalkyl})$ ” represent a haloalkyl group as defined above attached through an oxygen linkage ( $-\text{O}-$ ). For example, “ $\text{C}_{1-4}$  haloalkoxy” is intended to include  $\text{C}_1$ ,  $\text{C}_2$ ,  $\text{C}_3$ , and  $\text{C}_4$  haloalkoxy groups.

The terms “fluoroalkoxy” and “ $-\text{O}(\text{fluoroalkyl})$ ” represent a fluoroalkyl group as defined above attached through an oxygen linkage ( $-\text{O}-$ ). For example, “ $\text{C}_{1-4}$  fluoroalkoxy” is intended to include  $\text{C}_1$ ,  $\text{C}_2$ ,  $\text{C}_3$ , and  $\text{C}_4$  fluoroalkoxy groups.

The term “carbocyclo”, “carbocyclic”, or “carbocyclyl” may be used interchangeably and refer to cyclic groups having at least one saturated or partially saturated non-aromatic ring wherein all atoms of all rings are carbon. The carbocyclyl ring may be unsubstituted or may contain one or more substituents as valence allows. Thus, the term includes nonaromatic rings such as, for example, cycloalkyl, cycloalkenyl, and cycloalkynyl rings. Exemplary bicyclic carbocyclyl groups include, indanyl, indenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, hexahydronaphthalenyl,

octahydronaphthalenyl, decahydronaphthalenyl, bicycloheptanyl, bicyclooctanyl, and bicyclononyl.

The term “aryl” as used herein, refers to a group of atoms derived from a molecule containing aromatic ring(s) by removing one hydrogen that is bonded to the aromatic ring(s). Heteroaryl groups that have two or more rings must include only aromatic rings. Representative examples of aryl groups include, but are not limited to, phenyl and naphthyl. The aryl ring may be unsubstituted or may contain one or more substituents as valence allows.

The term “benzyl”, as used herein, refers to a methyl group in which one of the hydrogen atoms is replaced by a phenyl group. The phenyl ring may be unsubstituted or may contain one or more substituents as valence allows.

The term “heteroatom” refers to oxygen (O), sulfur (S), and nitrogen (N).

The term “heterocyclo”, “heterocyclic”, or “heterocyclyl” may be used interchangeably and refer to cyclic groups having at least saturated or partially saturated non-aromatic ring and wherein one or more of the rings have at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1 to 3 heteroatoms independently selected from O, S, and/or N. The ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may be unsubstituted or may contain one or more substituents as valence allows.

Exemplary monocyclic heterocyclyl groups include pyrrolidinyl, imidazolyl, oxazolidinyl, isoxazolyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane, tetrahydro-1,1-dioxothienyl, dihydroisoindolyl, and tetrahydroquinolyl.

The term “heteroaryl” refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups that have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms independently selected from O, S, and/or N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic group are aromatic and may contain only carbon atoms. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Bicyclic heteroaryl groups must include only aromatic rings. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may be unsubstituted or may contain one or more substituents.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thiophenyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl.



Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinoliny, tetrahydroisoquinoliny, isoquinoliny, benzimidazolyl, benzopyranly, indoliziny, benzofuranyl, chromonyl, coumariny, benzopyranly, cinnoliny, quinoxaliny, indazolyl, and pyrrolopyridyl.

The term “spirocarbocyclo”, “spirocarbocyclic”, or “spirocarbocyclyl” refers to a carbocyclyl ring attached to the molecular moiety by a carbon atom in the carbocyclyl ring that is shared with the molecular moiety.

The term “spiroheterocyclo”, “spiroheterocyclic”, or “spiroheterocyclyl” refers to a heterocyclyl ring attached to the molecular moiety by a carbon atom in the heterocyclyl ring that is shared with the molecular moiety.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The compounds of Formula (I) can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds of Formula (I) as amorphous solids.

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula (I) are also within the scope of the present invention. The term “solvate” means a physical association of a compound of Formula (I) with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanlates, methanlates, isopropanolates, acetonitrile solvates, and ethyl acetate solvates. Methods of solvation are known in the art.

Various forms of prodrugs are well known in the art and are described in:

a) Wermuth, C. G. et al., *The Practice of Medicinal Chemistry*, Chapter 31, Academic Press (1996);

b) Bundgaard, H. ed., *Design of Prodrugs*, Elsevier (1985);

c) Bundgaard, H., Chapter 5: “Design and Application of Prodrugs”, *A Textbook of Drug Design and Development*, pp. 113-191, Krogsgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991); and

d) Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism*, Wiley-VCH (2003).

In addition, compounds of Formula (I), subsequent to their preparation, can be isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of a compound of Formula (I) (“substantially pure”), which is then used or formulated as described herein. Such “substantially pure” compounds of Formula (I) are also contemplated herein as part of the present invention.

“Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

“Therapeutically effective amount” is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combi-

nation with other active ingredients effective to act as an inhibitor to TNF $\alpha$ , or effective to treat or prevent autoimmune and/or inflammatory disease states, such as multiple sclerosis and rheumatoid arthritis.

As used herein, “treating” or “treatment” cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

The compounds of the present invention are intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of carbon include <sup>13</sup>C and <sup>14</sup>C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. For example, methyl (—CH<sub>3</sub>) also includes deuterated methyl groups such as —CD<sub>3</sub>.

Compounds in accordance with Formula (I) can be administered by any means suitable for the condition to be treated, which can depend on the need for site-specific treatment or quantity of Formula (I) compound to be delivered.

Also embraced within this invention is a class of pharmaceutical compositions comprising a compound of Formula (I) and one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as “carrier” materials) and, if desired, other active ingredients. The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, and intrasternally in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g., magnesium stearate and a disintegrating agent such as croscopovidone. The carrier mixture may be filled into a gelatin capsule or compressed as a tablet. The pharmaceutical composition may be administered as an oral dosage form or an infusion, for example.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, liquid capsule, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. For example, the pharmaceutical composition may be provided as a tablet or capsule comprising an amount of active ingredient in the range of from about 0.1 to 1000 mg, preferably from about 0.25 to 250 mg, and more preferably from about 0.5 to 100 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, can be determined using routine methods.



Any pharmaceutical composition contemplated herein can, for example, be delivered orally via any acceptable and suitable oral preparations. Exemplary oral preparations, include, but are not limited to, for example, tablets, troches, lozenges, aqueous and oily suspensions, dispersible powders or granules, emulsions, hard and soft capsules, liquid capsules, syrups, and elixirs. Pharmaceutical compositions intended for oral administration can be prepared according to any methods known in the art for manufacturing pharmaceutical compositions intended for oral administration. In order to provide pharmaceutically palatable preparations, a pharmaceutical composition in accordance with the invention can contain at least one agent selected from sweetening agents, flavoring agents, coloring agents, demulcents, anti-oxidants, and preserving agents.

A tablet can, for example, be prepared by admixing at least one compound of Formula (I) with at least one non-toxic pharmaceutically acceptable excipient suitable for the manufacture of tablets. Exemplary excipients include, but are not limited to, for example, inert diluents, such as, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as, for example, microcrystalline cellulose, sodium croscarmellose, corn starch, and alginic acid; binding agents, such as, for example, starch, gelatin, polyvinyl-pyrrolidone, and acacia; and lubricating agents, such as, for example, magnesium stearate, stearic acid, and talc. Additionally, a tablet can either be uncoated, or coated by known techniques to either mask the bad taste of an unpleasant tasting drug, or delay disintegration and absorption of the active ingredient in the gastrointestinal tract thereby sustaining the effects of the active ingredient for a longer period. Exemplary water soluble taste masking materials, include, but are not limited to, hydroxypropyl-methylcellulose and hydroxypropyl-cellulose. Exemplary time delay materials, include, but are not limited to, ethyl cellulose and cellulose acetate butyrate.

Hard gelatin capsules can, for example, be prepared by mixing at least one compound of Formula (I) with at least one inert solid diluent, such as, for example, calcium carbonate; calcium phosphate; and kaolin.

Soft gelatin capsules can, for example, be prepared by mixing at least one compound of Formula (I) with at least one water soluble carrier, such as, for example, polyethylene glycol; and at least one oil medium, such as, for example, peanut oil, liquid paraffin, and olive oil.

An aqueous suspension can be prepared, for example, by admixing at least one compound of Formula (I) with at least one excipient suitable for the manufacture of an aqueous suspension. Exemplary excipients suitable for the manufacture of an aqueous suspension, include, but are not limited to, for example, suspending agents, such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, alginic acid, polyvinyl-pyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as, for example, a naturally-occurring phosphatide, e.g., lecithin; condensation products of alkylene oxide with fatty acids, such as, for example, polyoxyethylene stearate; condensation products of ethylene oxide with long chain aliphatic alcohols, such as, for example, heptadecaethylene-oxycetanol; condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol, such as, for example, polyoxyethylene sorbitol monooleate; and condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, such as, for example, polyethylene sorbitan monooleate. An aqueous suspension can also contain

at least one preservative, such as, for example, ethyl and n-propyl p-hydroxybenzoate; at least one coloring agent; at least one flavoring agent; and/or at least one sweetening agent, including but not limited to, for example, sucrose, saccharin, and aspartame.

Oily suspensions can, for example, be prepared by suspending at least one compound of Formula (I) in either a vegetable oil, such as, for example, *arachis* oil; olive oil; sesame oil; and coconut oil; or in mineral oil, such as, for example, liquid paraffin. An oily suspension can also contain at least one thickening agent, such as, for example, beeswax; hard paraffin; and cetyl alcohol. In order to provide a palatable oily suspension, at least one of the sweetening agents already described hereinabove, and/or at least one flavoring agent can be added to the oily suspension. An oily suspension can further contain at least one preservative, including, but not limited to, for example, an anti-oxidant, such as, for example, butylated hydroxyanisole, and alpha-tocopherol.

Dispersible powders and granules can, for example, be prepared by admixing at least one compound of Formula (I) with at least one dispersing and/or wetting agent; at least one suspending agent; and/or at least one preservative. Suitable dispersing agents, wetting agents, and suspending agents are as already described above. Exemplary preservatives include, but are not limited to, for example, anti-oxidants, e.g., ascorbic acid. In addition, dispersible powders and granules can also contain at least one excipient, including, but not limited to, for example, sweetening agents; flavoring agents; and coloring agents.

An emulsion of at least one compound of Formula (I) thereof can, for example, be prepared as an oil-in-water emulsion. The oily phase of the emulsions comprising compounds of Formula (I) may be constituted from known ingredients in a known manner. The oil phase can be provided by, but is not limited to, for example, a vegetable oil, such as, for example, olive oil and *arachis* oil; a mineral oil, such as, for example, liquid paraffin; and mixtures thereof. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Suitable emulsifying agents include, but are not limited to, for example, naturally-occurring phosphatides, e.g., soy bean lecithin; esters or partial esters derived from fatty acids and hexitol anhydrides, such as, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, such as, for example, polyoxyethylene sorbitan monooleate. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. An emulsion can also contain a sweetening agent, a flavoring agent, a preservative, and/or an antioxidant. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The compounds of Formula (I) can, for example, also be delivered intravenously, subcutaneously, and/or intramuscularly via any pharmaceutically acceptable and suitable injectable form. Exemplary injectable forms include, but are not limited to, for example, sterile aqueous solutions comprising acceptable vehicles and solvents, such as, for



example, water, Ringer's solution, and isotonic sodium chloride solution; sterile oil-in-water microemulsions; and aqueous or oleaginous suspensions.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (i.e., CAPTISOL®), cosolvent solubilization (i.e., propylene glycol) or micellar solubilization (i.e., Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

A sterile injectable oil-in-water microemulsion can, for example, be prepared by 1) dissolving at least one compound of Formula (I) in an oily phase, such as, for example, a mixture of soybean oil and lecithin; 2) combining the Formula (I) containing oil phase with a water and glycerol mixture; and 3) processing the combination to form a microemulsion.

A sterile aqueous or oleaginous suspension can be prepared in accordance with methods already known in the art. For example, a sterile aqueous solution or suspension can be prepared with a non-toxic parenterally-acceptable diluent or solvent, such as, for example, 1,3-butane diol; and a sterile oleaginous suspension can be prepared with a sterile non-toxic acceptable solvent or suspending medium, such as, for example, sterile fixed oils, e.g., synthetic mono- or diglycerides; and fatty acids, such as, for example, oleic acid.

Pharmaceutically acceptable carriers, adjuvants, and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-alpha-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, polyethoxylated castor oil such as CREMOPHOR® surfactant (BASF), or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as alpha-, beta-, and gamma-cyclodex-

trin, or chemically modified derivatives such as hydroxy-alkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions can be presented in a pack or dispenser device which can contain one or more unit dosage forms including the compound of Formula (I). The pack can, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The amounts of compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex, the medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.001 to 100 mg/kg body weight, preferably between about 0.0025 and about 50 mg/kg body weight and most preferably between about 0.005 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. Other dosing schedules include one dose per week and one dose per two day cycle.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

Pharmaceutical compositions of this invention comprise at least one compound of Formula (I) and optionally an additional agent selected from any pharmaceutically acceptable carrier, adjuvant, and vehicle. Alternate compositions of this invention comprise a compound of the Formula (I) described herein, or a prodrug thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

The pharmaceutical compositions may contain other therapeutic agents and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (e.g., excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.



The compounds of the invention modulate the activity of TNF $\alpha$ . Accordingly, compounds of Formula (I) have utility in treating conditions associated with the modulation of TNF $\alpha$ .

The compounds in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments. The compounds in accordance with the present invention can be beneficial either as a stand-alone therapy or in combination with other therapies that therapeutically could provide greater benefit. The ailments for which the compounds in the present invention could be of benefit include autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

Inflammatory and autoimmune disorders include systemic autoimmune disorders, autoimmune endocrine disorders and organ-specific autoimmune disorders. Systemic autoimmune disorders include systemic lupus erythematosus, psoriasis, psoriatic arthropathy, vasculitis, polymyositis, scleroderma, multiple sclerosis, systemic sclerosis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, non-specific inflammatory arthritis, juvenile inflammatory arthritis, juvenile idiopathic arthritis (including oligoarticular and polyarticular forms thereof), anemia of chronic disease, Still's disease (juvenile and/or adult onset), Behcet's disease and Sjögren's syndrome. Autoimmune endocrine disorders include thyroiditis. Organ-specific autoimmune disorders include Addison's disease, hemolytic or pernicious anemia, acute kidney injury, diabetic nephropathy, obstructive uropathy (including cisplatin-induced obstructive uropathy), glomerulonephritis (including Goodpasture's syndrome, immune complex-mediated glomerulonephritis and antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis), lupus nephritis, minimal change disease, Graves' disease, idiopathic thrombocytopenic purpura, inflammatory bowel disease (including Crohn's disease, ulcerative colitis, indeterminate colitis and pouchitis), pemphigus, atopic dermatitis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune pneumonitis, autoimmune carditis, myasthenia gravis, spontaneous infertility, osteoporosis, osteopenia, erosive bone disease, chondritis, cartilage degeneration and/or destruction, fibrosing disorders (including various forms of hepatic and pulmonary fibrosis), asthma, rhinitis, chronic obstructive pulmonary disease, respiratory distress syndrome, sepsis, fever, muscular dystrophy (including Duchenne muscular dystrophy), and organ transplant rejection (including kidney allograft rejection).

Neurological and neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, ischemia, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma, seizures, and epilepsy.

Cardiovascular disorders include thrombosis, cardiac hypertrophy, hypertension, irregular contractility of the heart (e.g., during heart failure), and myocardial infarction.

Metabolic disorders include diabetes (including insulin-dependent diabetes mellitus and juvenile diabetes), dyslipidemia, and metabolic syndrome.

Ocular disorders include retinopathy (including diabetic retinopathy, proliferative retinopathy, non-proliferative retinopathy and retinopathy of prematurity), macular edema (including diabetic macular edema), age-related macular degeneration, vascularization (including corneal vascularization and neovascularization), retinal vein occlusion, and various forms of uveitis and keratitis.

Oncological disorders, which may be acute or chronic, include proliferative disorders, especially cancer, and cancer-associated complications (including skeletal complications, cachexia and anemia). Particular categories of cancer include hematological malignancy (including leukemia and lymphoma) and non-hematological malignancy (including solid tumor cancer, sarcoma, meningioma, glioblastoma multiform, neuroblastoma, melanoma, gastric carcinoma, and renal cell carcinoma). Chronic leukemia may be myeloid or lymphoid.

One embodiment provides a method of treating a disorder selected from autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders, comprising administering to a mammalian patient in need of treatment, a compound according to claim 1 or a pharmaceutically acceptable salt thereof. Preferably, the patient is human. For example, a therapeutically effective amount for treating a disorder may be administered in the method of the present embodiment.

One embodiment provides a method of treating a disease or disorder associated with the activity of TNF $\alpha$ , comprising administering to a mammalian patient in need of treatment, a compound according to claim 1 or a pharmaceutically acceptable salt thereof. Preferably, the patient is human. For example, a therapeutically effective amount for treating a disorder may be administered in the method of the present embodiment.

One embodiment provides the compounds of Formula (I) for use in therapy. In the present embodiment, the use in therapy may include the administration of a therapeutically-effective amount of a compound of Formula (I).

The present invention also provides the use of the compounds of Formula (I) for the manufacture of a medicament for the treatment or prophylaxis of an allergic disorder and/or autoimmune and/or inflammatory disease. In the present embodiment, the use for the manufacture of a medicament may include the administration of a therapeutically-effective amount of a compound of Formula (I) for the treatment or prophylaxis of an allergic disorder and/or autoimmune and/or inflammatory disease.

The present invention also provides the use of the compounds of Formula (I) for the manufacture of a medicament for treatment of cancer. The present embodiment may include the use for the manufacture of a medicament includes the administration of a therapeutically-effective amount of a compound of Formula (I) for the treatment of cancer.

The present invention provides the use of compounds of Formula (I) as pharmacological tools in the search for new pharmacological agents or in the development of new biological assays. In one embodiment, the compounds of Formula (I) are useful as radioligands or can be coupled to a fluorophore and utilized in assays to identify pharmacologically active compounds.

In one embodiment, the compounds of Formula (I) inhibit TNF $\alpha$  functional activity with IC<sub>50</sub> values of less than 10  $\mu$ M, for example, from 0.001 to less than 10  $\mu$ M, as measured by the TNF induced HEK-Blue assay. Preferably, the compounds of Formula (I) inhibit TNF $\alpha$  functional activity with IC<sub>50</sub> values of less than 1  $\mu$ M, for example, from 0.001 to less than 1  $\mu$ M. Other preferred compounds inhibit TNF $\alpha$  functional activity with IC<sub>50</sub> values of 100 nM and less, for example, from 1 to 100 nM.



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Examples of compounds of Formula (I) as specified in the “Examples” section below, have been tested in one or more of the assays described below.

#### Methods of Preparation

The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry. General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Examples of compounds of the present invention prepared by methods described in the general schemes are given in the preparations and examples section set out hereinafter. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products.

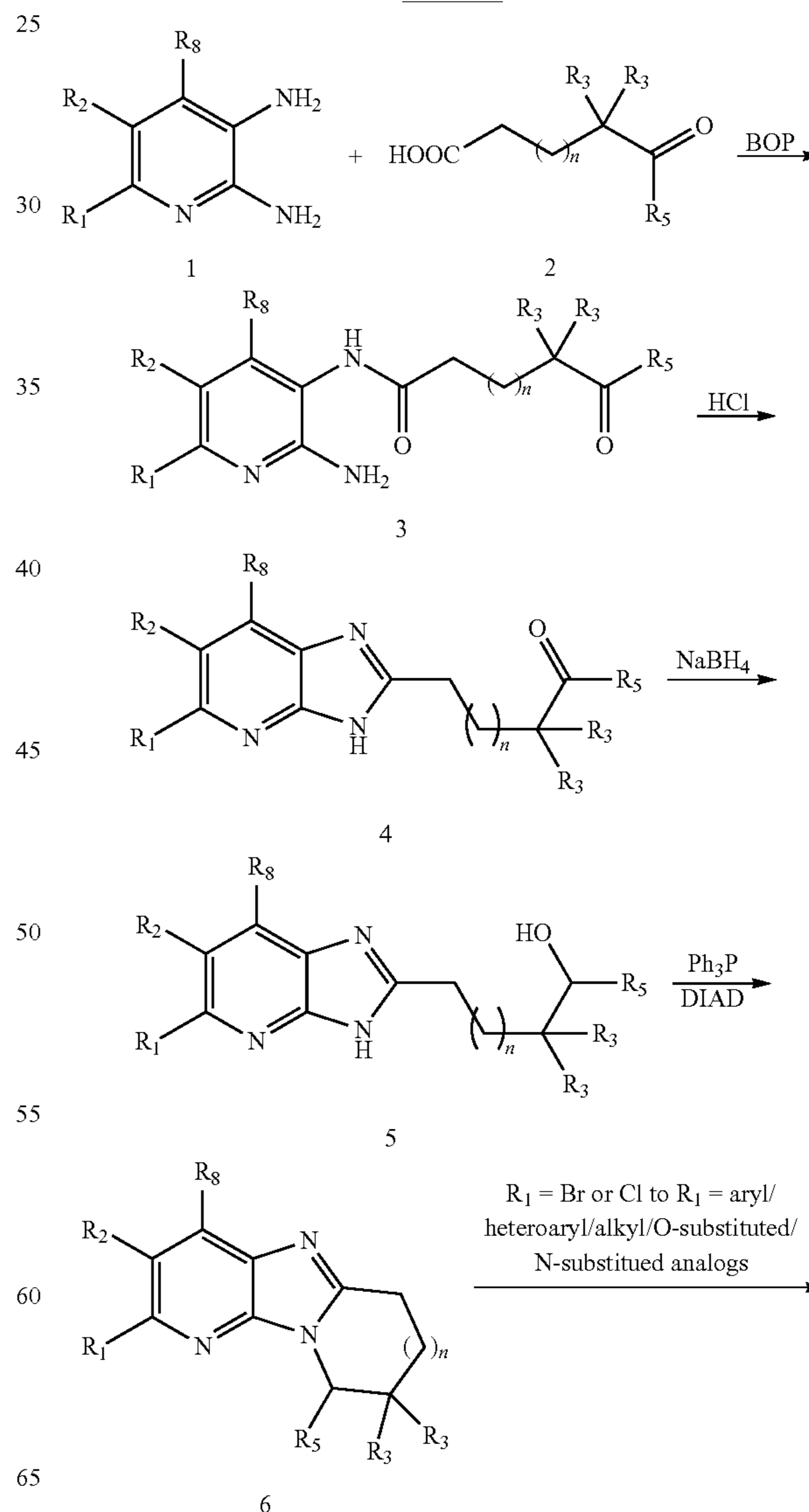
The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Third Edition, Wiley and Sons (1999)).

Scheme 1 illustrates a general synthesis of compound 7. Appropriately functionalized pyridine-1,2-diamine 1 can be reacted with functionalized ketoacid 2 using a coupling agent such as BOP in a solvent such as dichloromethane or N,N-dimethylformamide to provide amide Intermediate 3. Cyclization of 3 to benzimidazole 4 can be accomplished with an acid such as HCl. Compound 4 can be converted to alcohol 5 with a reducing agent such as NaBH<sub>4</sub>. Treatment of alcohol 5 with triphenylphosphine and diisopropyl azodicarboxylate in a solvent such as THF can afford desired tricyclic compound 6. When R<sub>1</sub> is Br or Cl, compound 6 can

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be converted to aryl, heteroaryl, alkyl, O-substituted or N-substituted analogs 7 by employing well established synthetic protocols in the literature—for example, the Suzuki-Miyaura cross-coupling reaction for the introduction of aryl and heteroaryl groups (*Chem. Soc. Rev.*, 42:5270 (2013)); alkyl groups may be introduced using the Greg Fu modified Suzuki-Miyaura cross-coupling methods (*J. Am. Chem. Soc.*, 124:13662 (2002) and *J. Am. Chem. Soc.*, 126:1340 (2004)); O- and N-substituted analogs may be introduced, for example, employing the Buchwald-Hartwig protocol (*Aldrichimica Acta*, 45:59 (2012) and *Synlett*, 268 (2011)) or may be added by nucleophilic substitution. Compounds of type 2 in Scheme 1 may be prepared, for example, by employing (a) Friedel-Crafts reaction of substituted or unsubstituted succinic anhydride with an aryl or heteroaryl moiety (R<sub>5</sub>=aryl or heteroaryl) or (b) addition of an Grignard reagent (R<sub>5</sub>-MgBr) or R<sub>5</sub>-Li to a substituted or unsubstituted succinic anhydride.

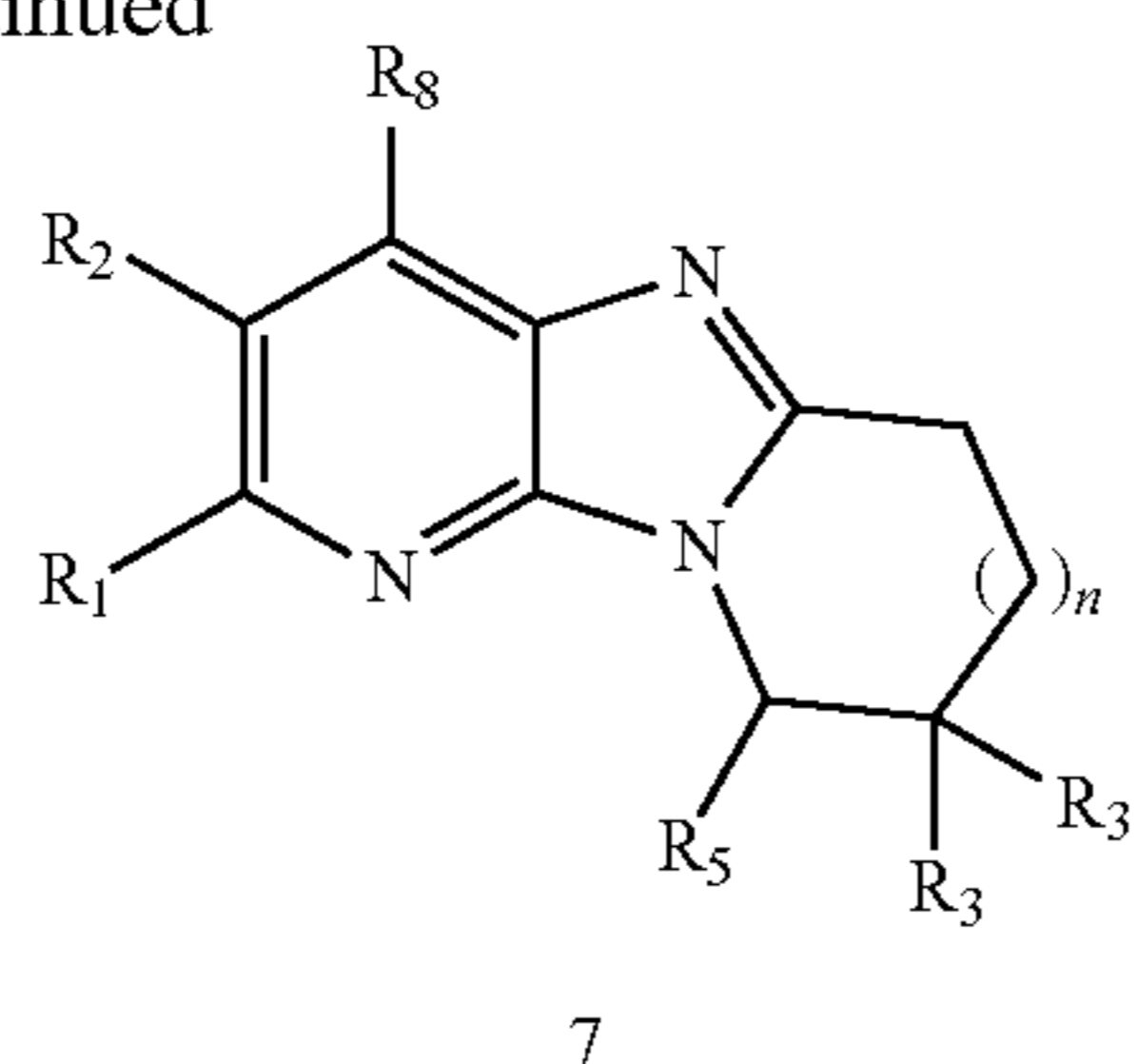
Scheme 1





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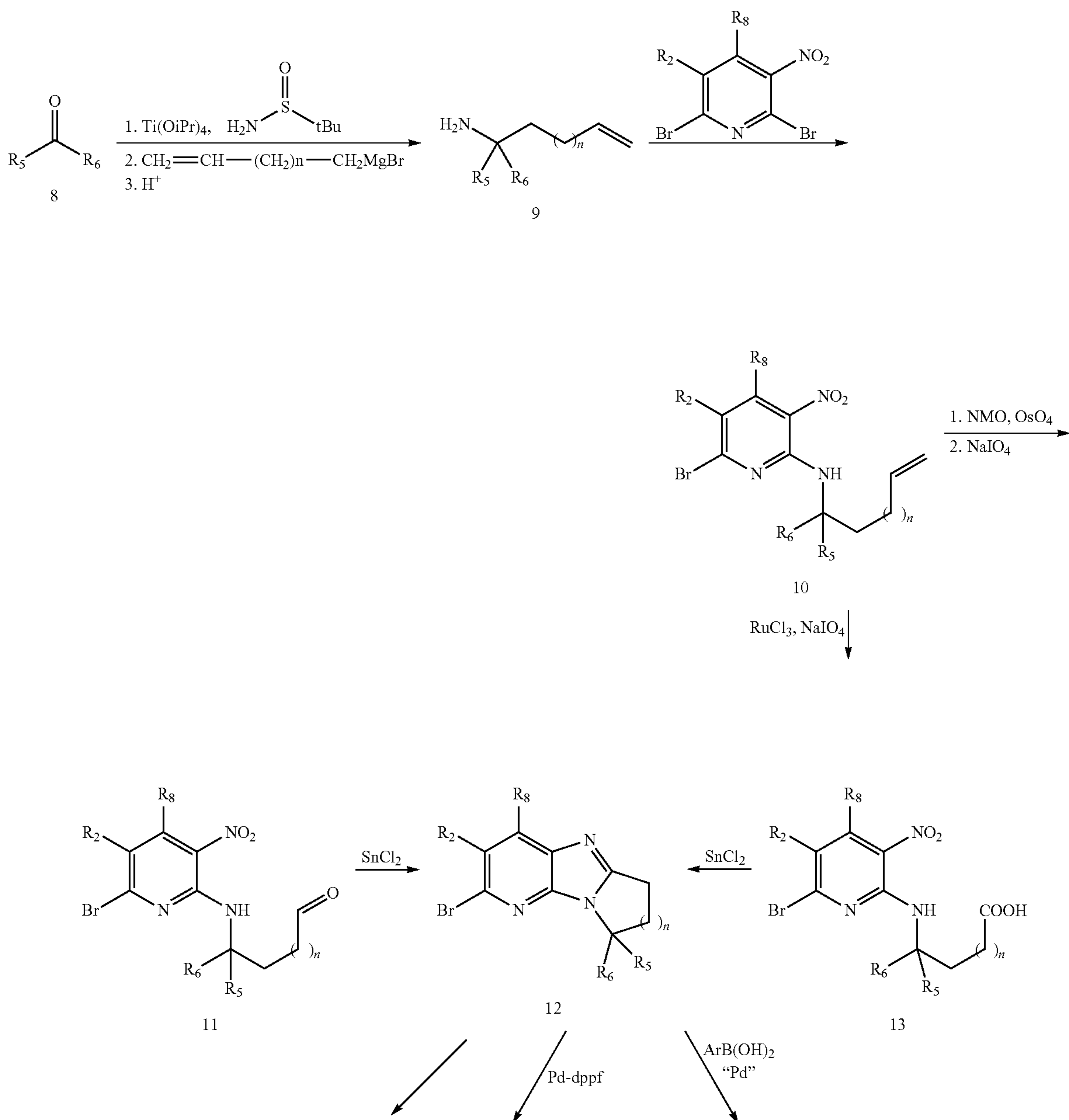


Scheme 2 illustrates a regioselective approach to the synthesis of compounds of type 15. Appropriately functionalized aldehydes or ketones 8 may be converted to amines 9 employing the Ellman protocol (*Chem. Rev.*, 110:3600

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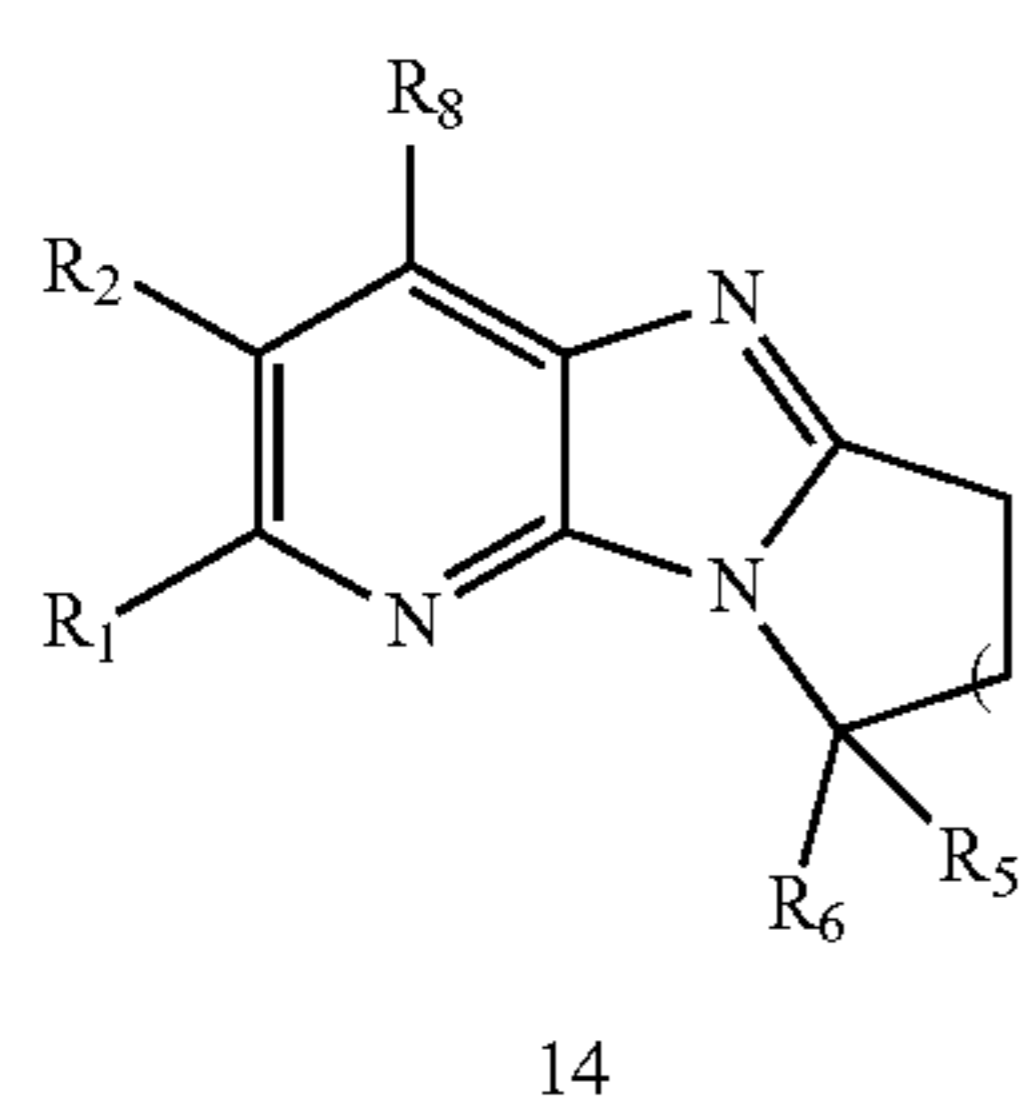
(2010))—sulfonamide imine formation, Grignard reaction, and hydrolysis. The amine 9 can react with a substituted a dibromonitropyridine to give compound 10. Compound 10 may be oxidized to aldehyde 11 through ozonolysis or NMO/OsO<sub>4</sub>/NaIO<sub>4</sub> method. Treatment of the aldehyde 11 with SnCl<sub>2</sub> can give the tricyclic compound 12 in one step. Alternatively, oxidation of the double bond in compound 10 by sodium periodate in the presence of ruthenium(III) chloride, followed by tin(II) chloride reduction of the crude product and in situ cyclization can give the tricyclic imidazole compound 12. Converting compound 12 to boronic ester 12a and then coupling of 12a with an aryl bromide can afford aryl or heteroaryl compounds 15. In addition, compound 12 may be converted to alkyl, O-substituted or N-substituted analogs 14 employing protocols described for compounds in Scheme 1.

Scheme 2

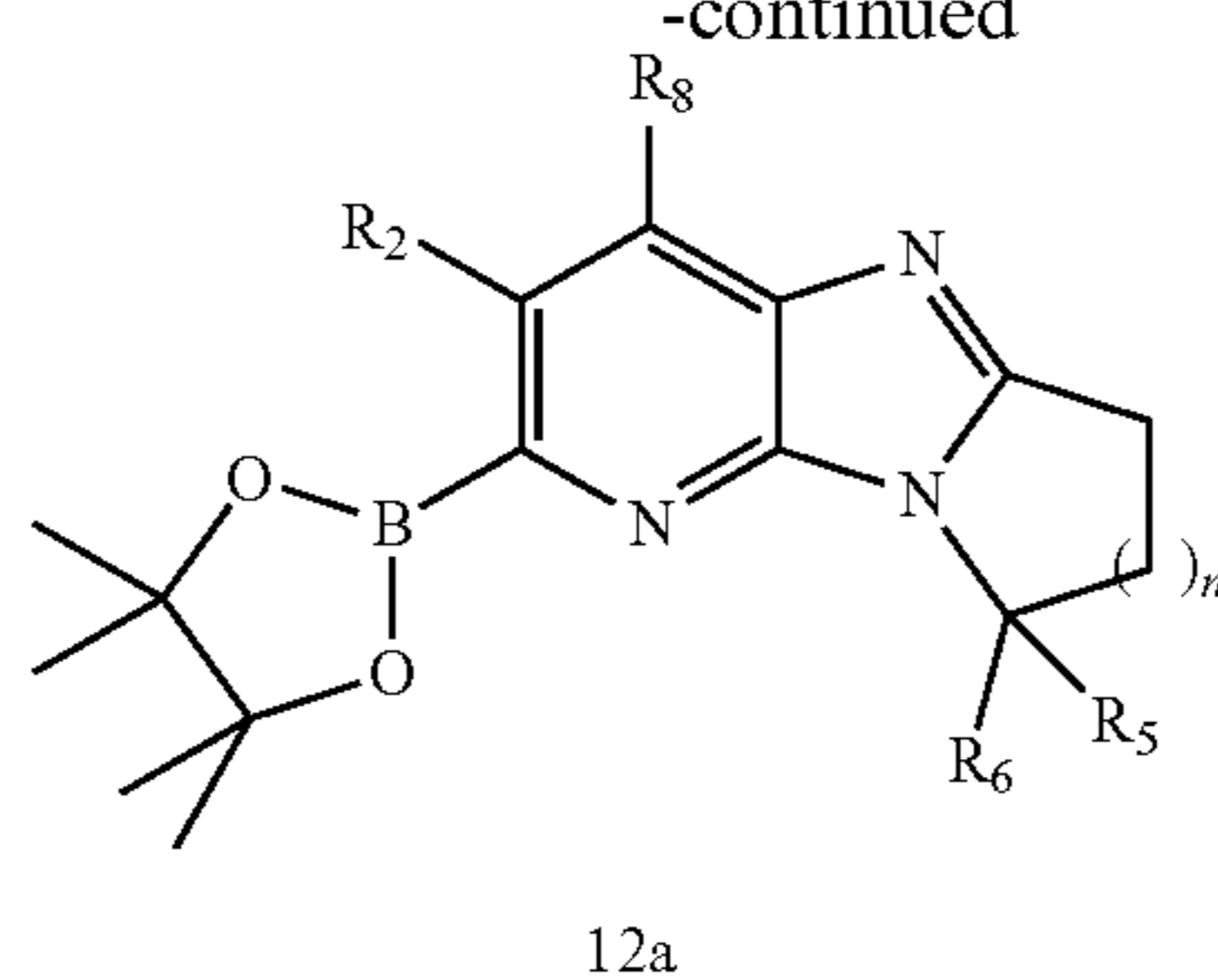




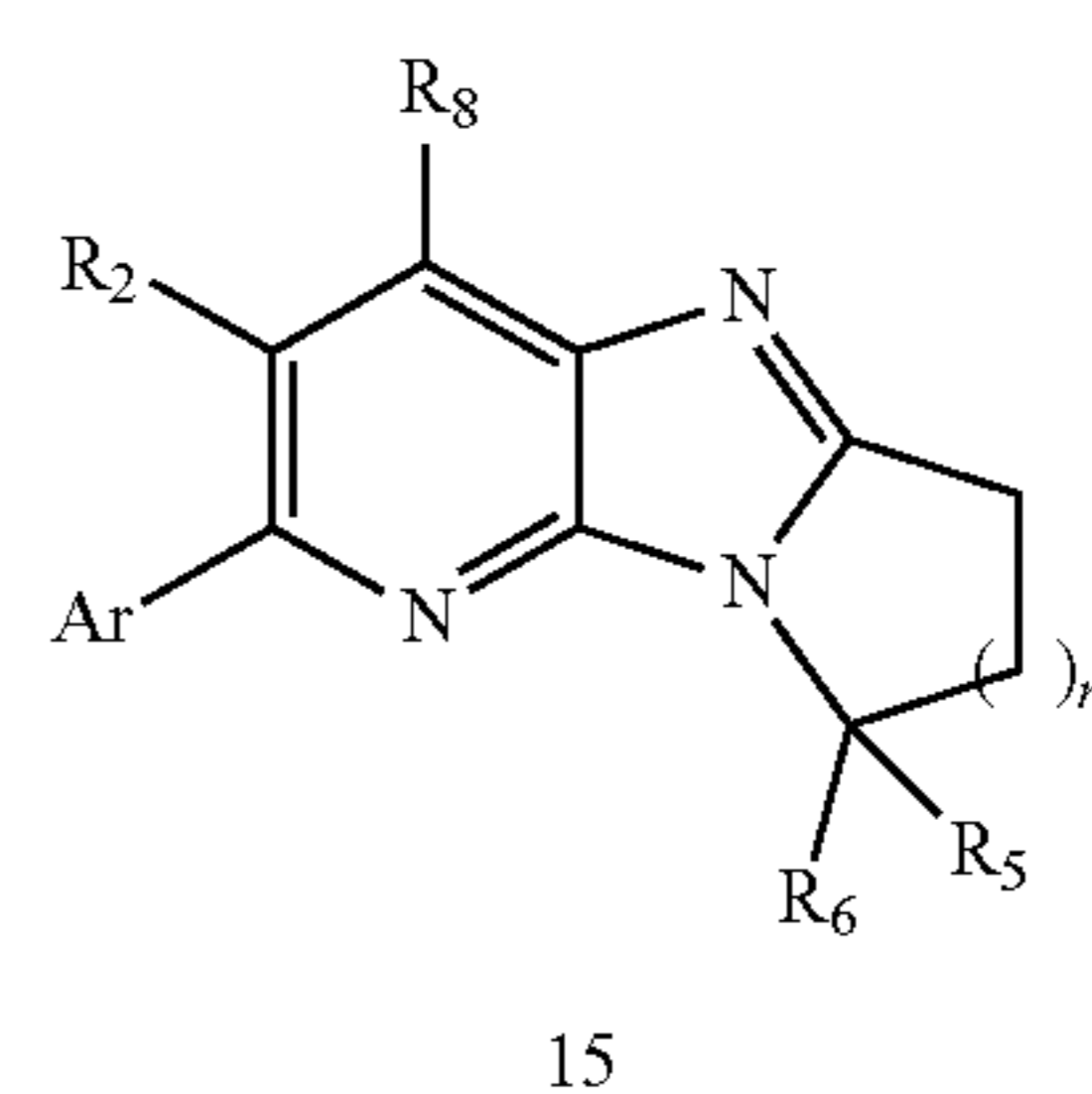
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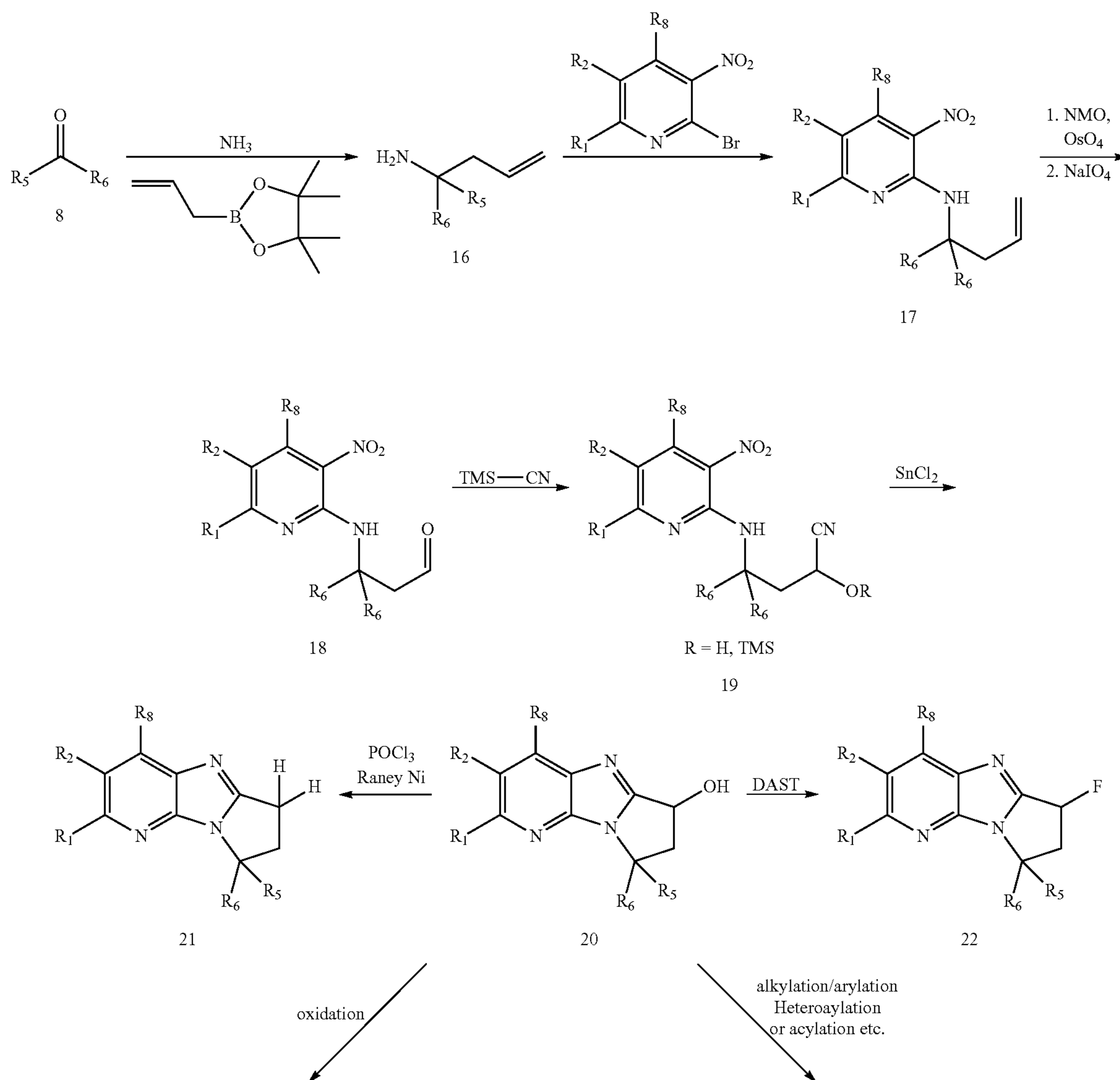
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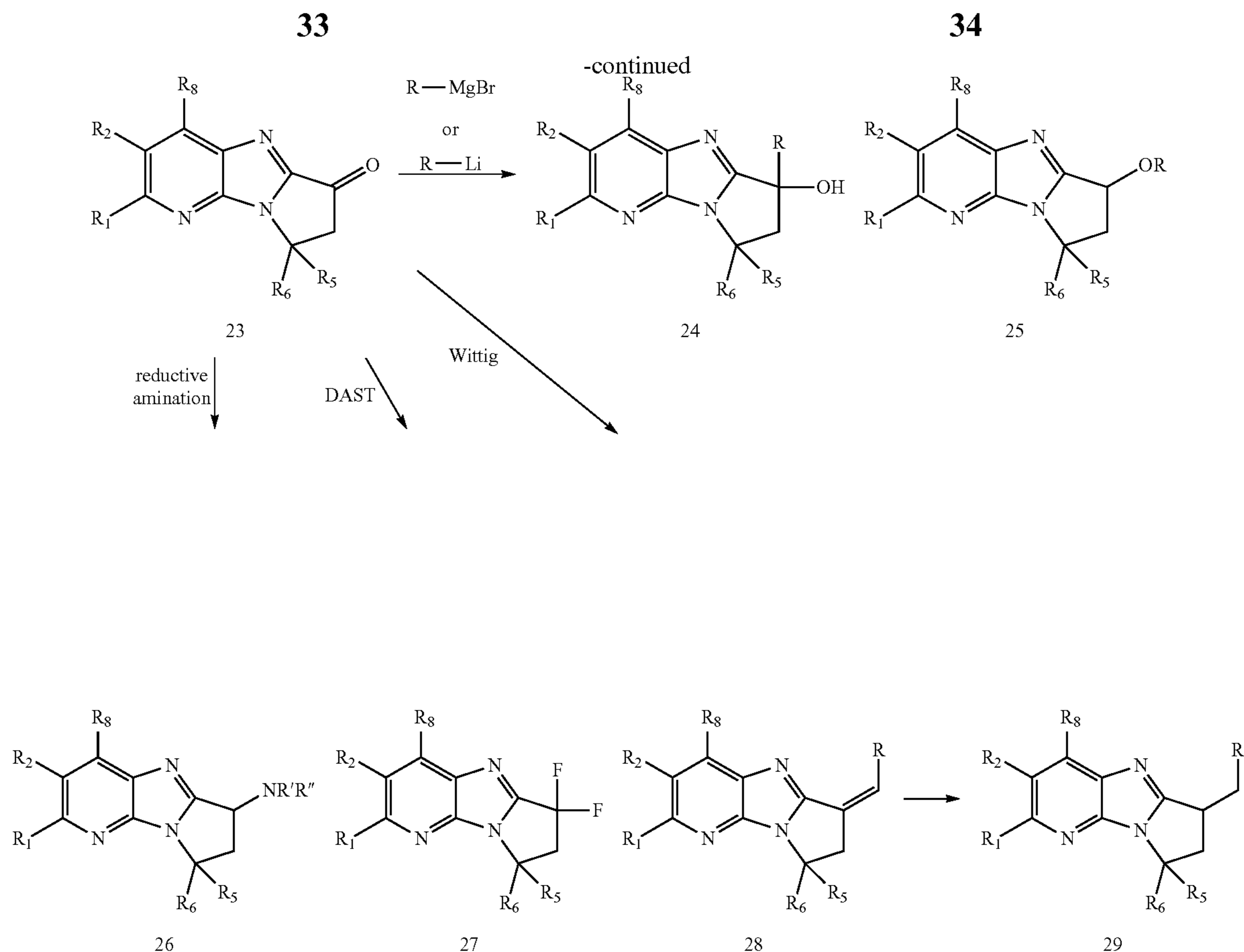
Scheme 3 illustrates approaches to synthesize ring substituted tricyclic compounds. Aldehyde or ketone 8 can react with allylboronic acid ester in the presence of ammonia to give amine 16 that can react with an appropriately substituted fluoronitrobenzene to give compound 17. Conversion of compound 17 to the aldehyde 18 can be achieved by treating with NMO in the presence of osmium tetroxide,

15 followed by sodium periodate. Treatment of the aldehyde 18 with trimethylsilyl cyanide in the presence of zinc iodide can give cyanohydrin product 19 which on reduction of the nitro group provides hydroxy tricyclic imidazole 20 in one step. Functional group transformations of the alcohol 20, may provide substituted tricyclic analogs (e.g., 21-29), as shown in Scheme 3.

Scheme 3



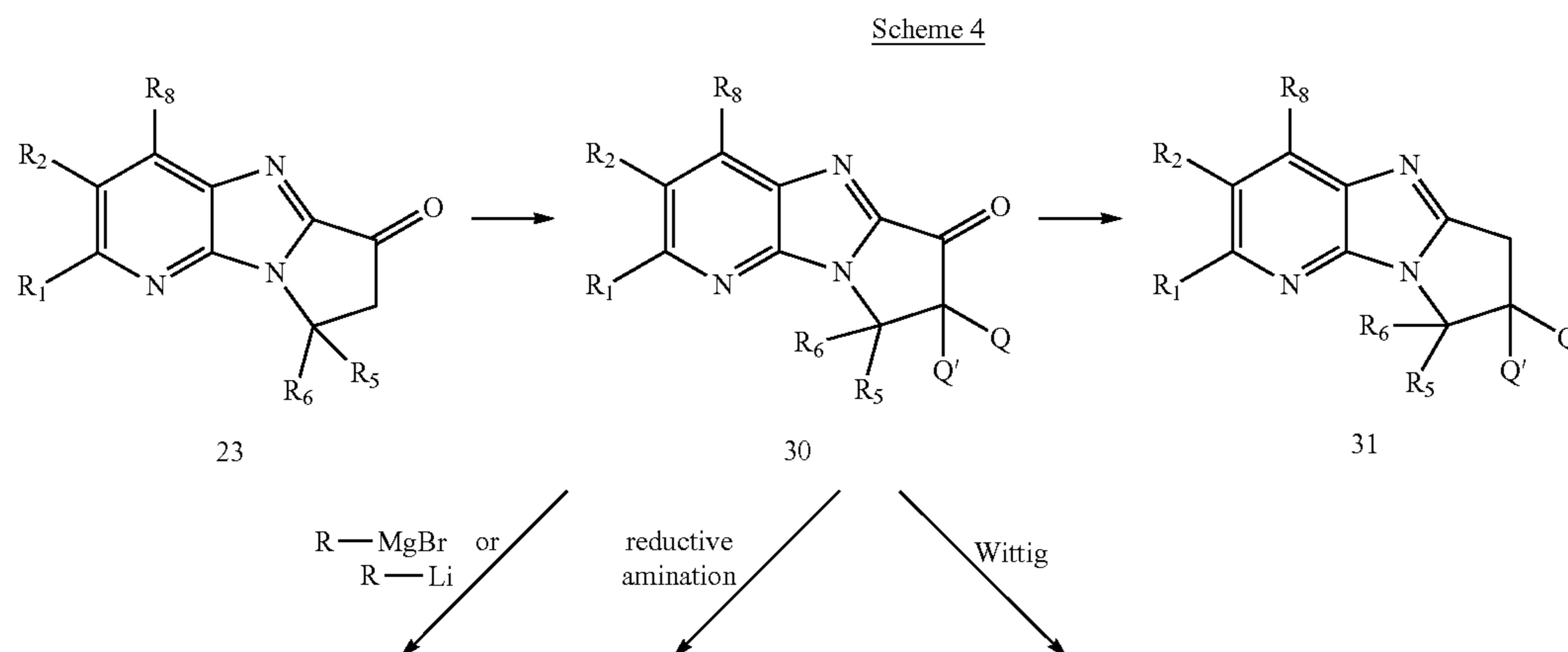




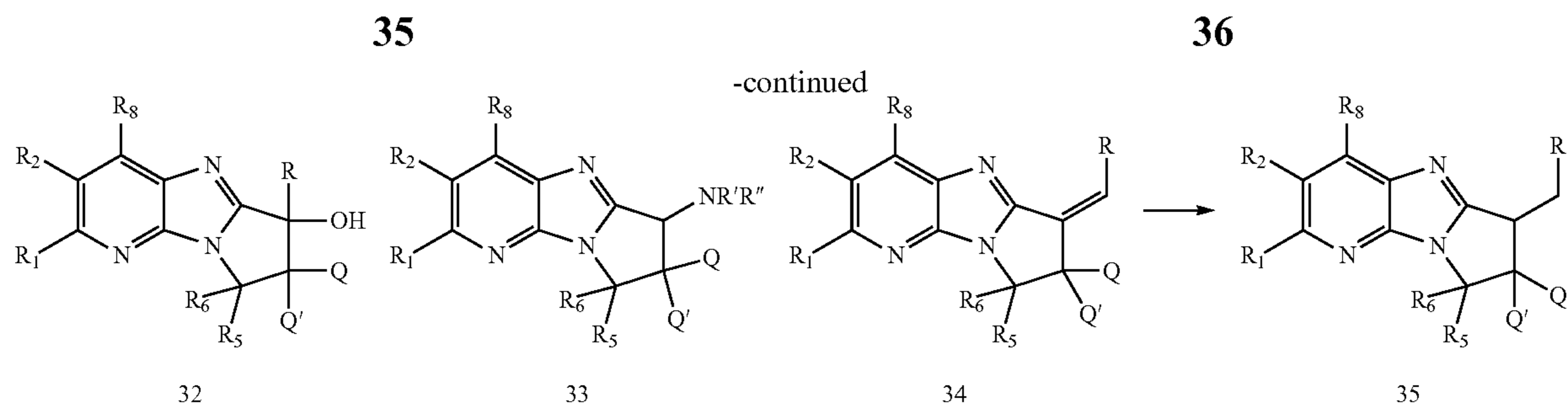
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Scheme 4 illustrates alternate approaches for the synthesis of substituted tricyclic compounds. Compound 23 can be functionalized adjacent to the carbonyl group employing procedures well documented in the literature. For example, treatment of compound 23 with a strong base such as lithium bis(trimethylsilyl)amide and an alkylating agent affords compounds of type 28 where Q, Q' can be an alkyl group. Alternatively,  $\alpha$ -hydroxy ketones (Q=H, Q'=OH) may be synthesized employing the Rubottom oxidation (*Tetrahedron Lett.*, 15:4319 (1974)) or employing the Davis oxaziridine reagent (*Synlett*, 23:2572 (2012)).  $\alpha$ -Amino ketones may be synthesized in a similar fashion (*J. Am. Chem. Soc.*, 135:16074 (2013)).  $\alpha$ -Aryl or heteroaryl ketones (Q=H,

Q'=aryl or heteroaryl) may be synthesized employing the Buchwald protocol (*J. Am. Chem. Soc.*, 119:11108 (1997)). The carbonyl group of compound 28 may be deoxygenated to compounds of the type 29 employing a Clemmensen Reduction or Wolff-Kishner Reduction or via a dithiane intermediate followed by treatment with Raney-Ni or using PMHS and FeCl<sub>3</sub> (*Synlett*, 276 (2009)) or by reduction to the hydroxyl group followed by deoxygenation, for example, using the Barton-McCombie reaction (*J. Chem. Soc. Perkin 1*, 1574 (1975)) and related methods (*Angew. Chem. Int. Ed.*, 51:2907-2911 (2012)). Functional group transformations of the ketone 28, may provide substituted tricyclic analogs (e.g., 30-35), as shown in Scheme 4.

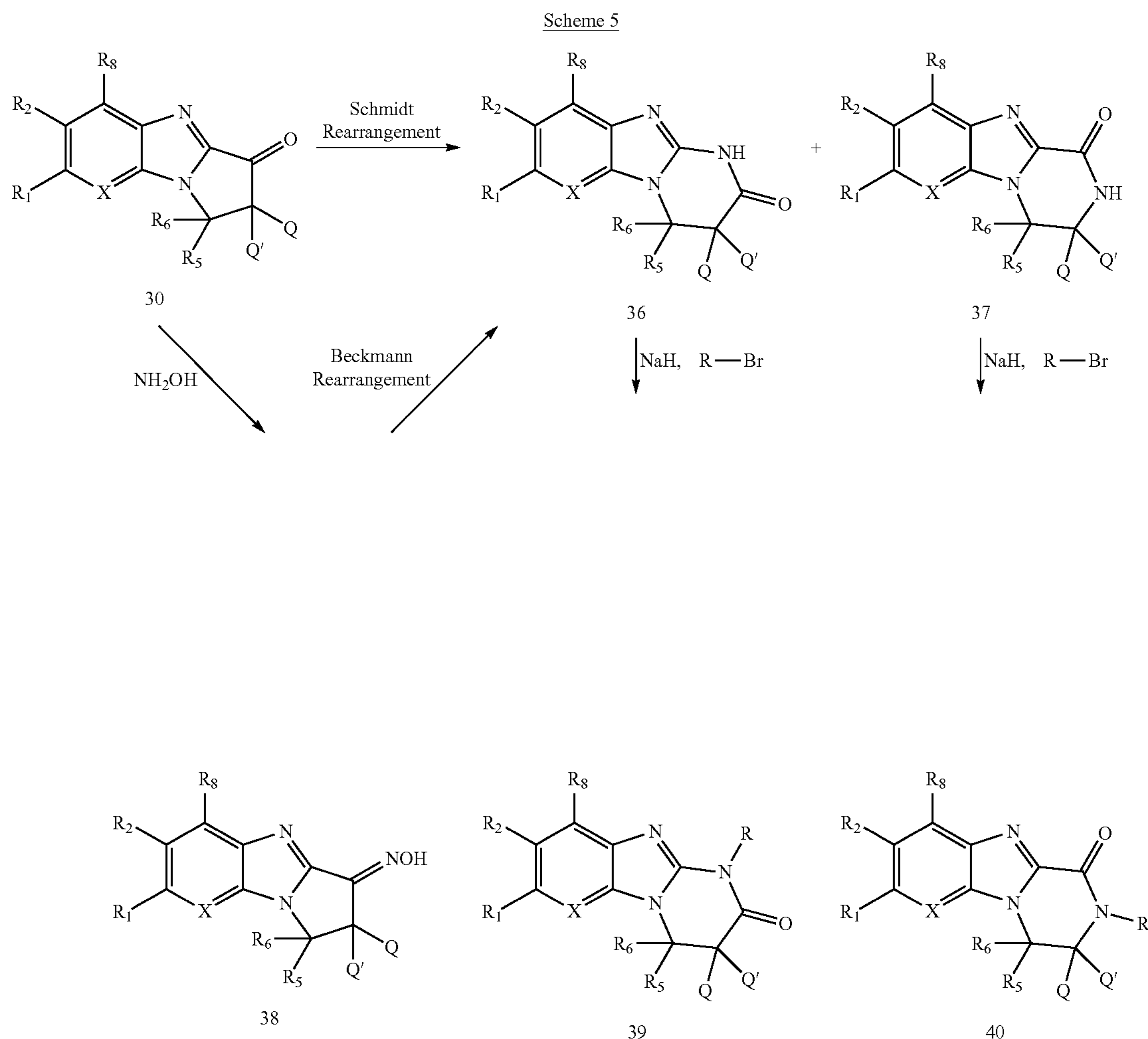






Scheme 5 illustrates approaches to synthesize a series of tricyclic compounds with a lactam moiety. Schmidt rearrangement of 30 under conditions such as hydrazoic acid and sulfuric acid will provide two possible rearrangement products 36 and 37. Alternatively, 30 can be converted to oxime 38 using hydroxylamine, which can be subjected to Beckmann rearrangement conditions to afford the same products 36 and 37. Both 36 and 37 can be further derivatized at the amide position by reacting with R—Br under basic conditions such as sodium hydride to give 39 and 40.

acids or esters 41 (either commercially available or readily prepared by hydrolysis of the chiral lactams 42 (*J. Org. Chem.*, 78:3647-3654 (2013))). 41 may be reacted with a 2,6-dibromonitropyridine to produce 43, which may be cyclized to lactam 44, which may be converted to 45 by reductive cyclization. Alternatively, lactam 44 can be produced by a copper mediated coupling of lactam 42 with a 2,6-dibromonitropyridine (*J. Org. Chem.*, 3863-3867

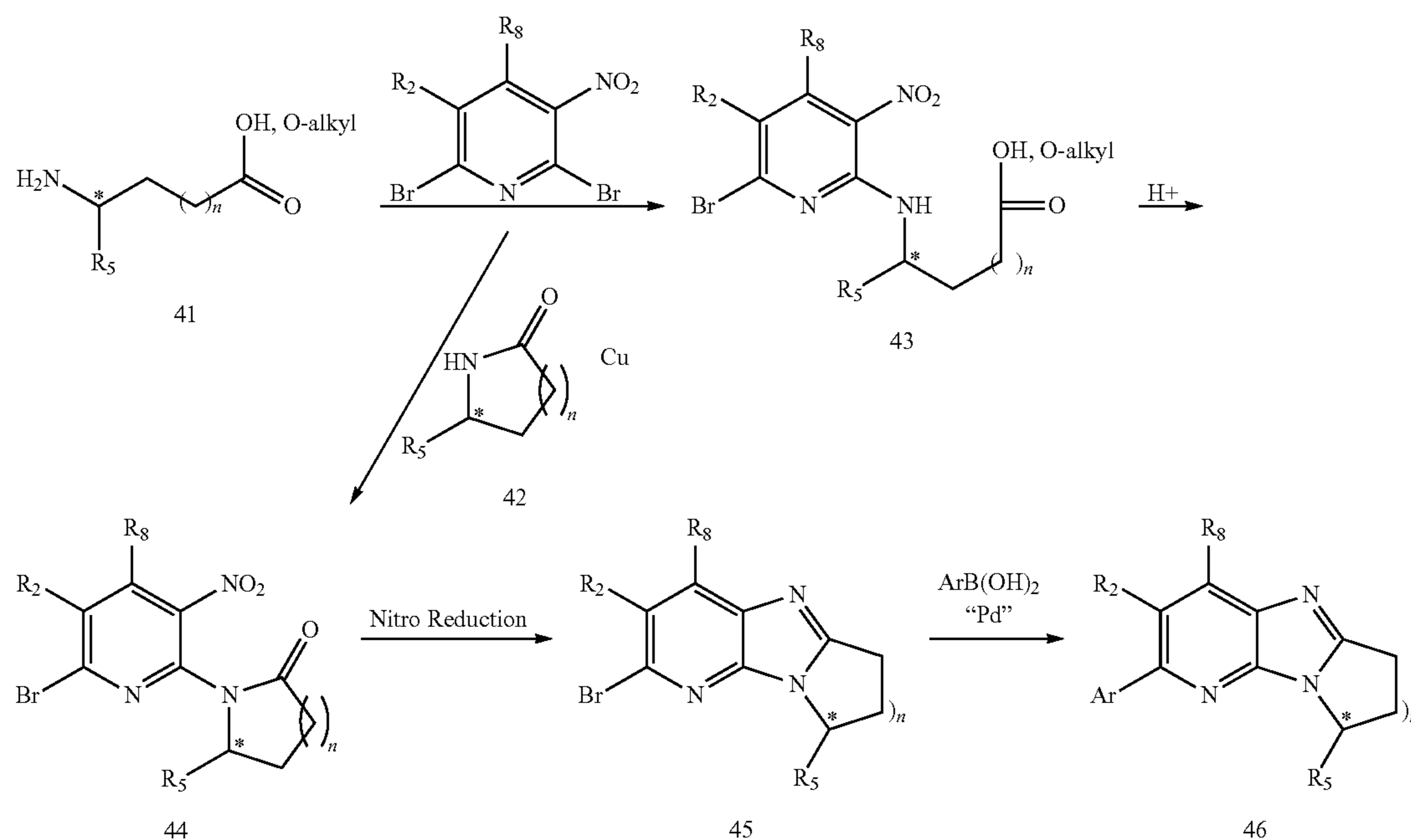


Scheme 6 illustrates alternative synthetic routes which in some instances will provide chiral compounds using appropriate starting materials such as chiral aminoarylalkanoic

(2007)). Additional functionalization of 45 by the well-known Suzuki-Miyaura cross coupling methods will provide 46.



Scheme 6



\*Chiral center, n = 1-2

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## Abbreviations

AcOH acetic acid  
 BOP benzotriazol-1-yloxytris-(dimethylamino)-phosphonium hexafluorophosphate  
 DCM dichloromethane  
 DIEA N,N-diisopropylethylamine  
 DMSO dimethyl sulfoxide  
 EtOAc ethyl acetate  
 Et<sub>2</sub>O diethyl ether  
 h hour(s)  
 HPLC High Pressure Liquid Chromatography  
 LC/MS Liquid Chromatography-Mass Spectroscopy  
 MeOH methanol  
 min minute(s)  
 mmol millimole(s)  
 NMO N-methylmorpholine-N-oxide  
 NMR nuclear magnetic resonance spectroscopy  
 PdCl<sub>2</sub>(dppf) [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)  
 Pd(Ph<sub>3</sub>P)<sub>4</sub> tetrakis(triphenylphosphine)palladium  
 TFA trifluoroacetic acid  
 THF tetrahydrofuran

## EXAMPLES

The following Examples illustrate the particular and preferred embodiments of the present invention and do not limit the scope of the present invention. Chemical abbreviations and symbols as well as scientific abbreviations and symbols have their usual and customary meanings unless otherwise specified. Additional abbreviations employed in the Examples and elsewhere in this application are defined above. Common intermediates are generally useful for the preparation of more than one Example and are identified sequentially (e.g., Intermediate 1, Intermediate 2, etc.) and

are abbreviated as Int. 1, Int. 2, etc. Compounds of the Examples are identified by the example and step in which they were prepared (e.g., "1-A" denotes the Example 1, step A), or by the example only where the compound is the title compound of the example (for example, "1" denotes the title compound of Example 1). In some instances alternate preparations of intermediates or examples are described. Frequently chemists skilled in the art of synthesis may devise alternative preparations which may be desirable based on one or more considerations such as shorter reaction time, less expensive starting materials, ease of operation, amenable to catalysis, avoidance of toxic reagents, accessibility of specialized instrumentation, and decreased number of linear steps, etc. The intent of describing alternative preparations is to further enable the preparation of the examples of this invention. In some instances some functional groups in the outlined examples and claims may be replaced by well-known bioisosteric replacements known in the art, for example, replacement of a carboxylic acid group with a tetrazole or a phosphate moiety.

## HPLC Conditions

Condition A: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

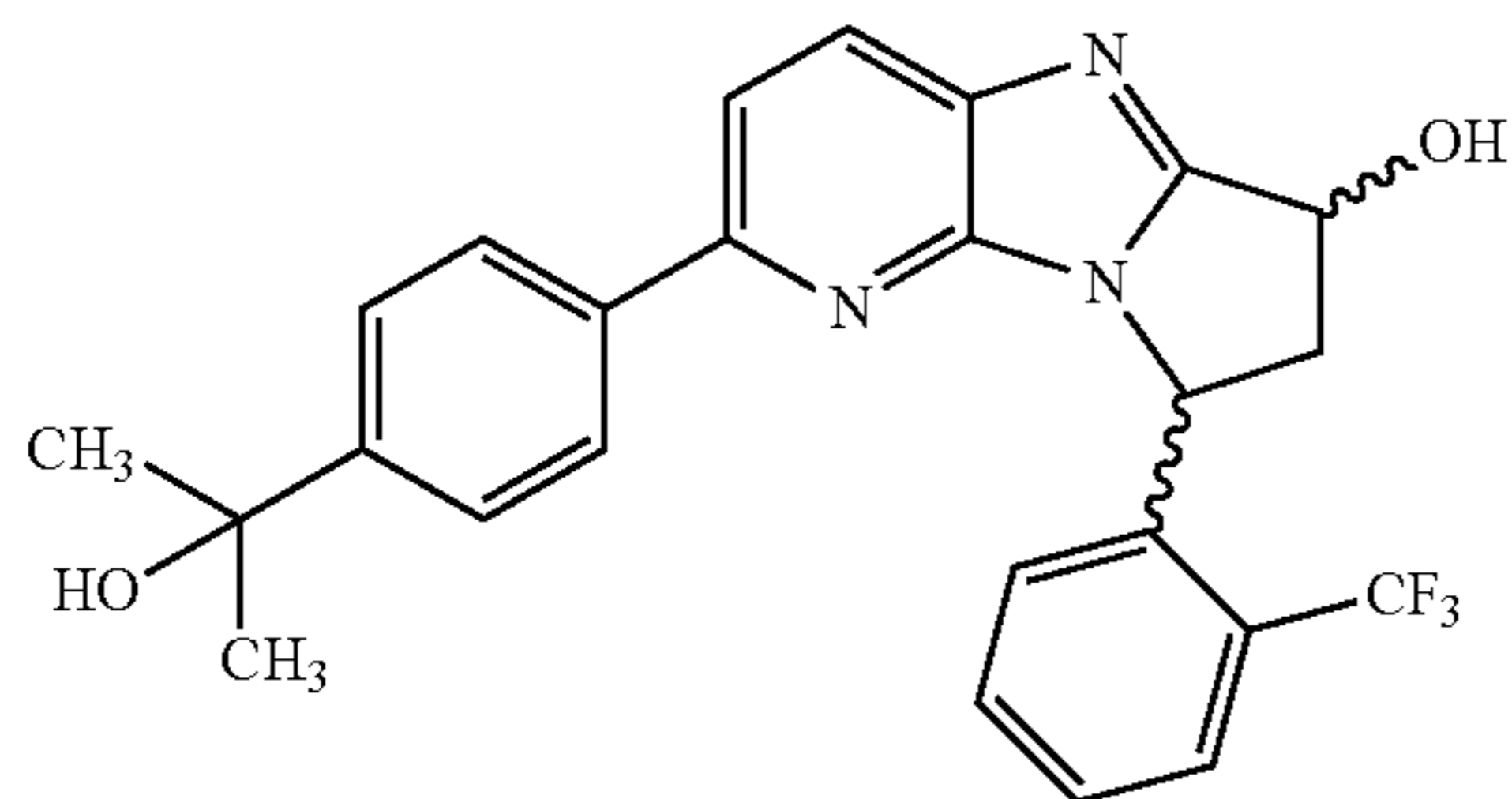
Condition B: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.



## 39

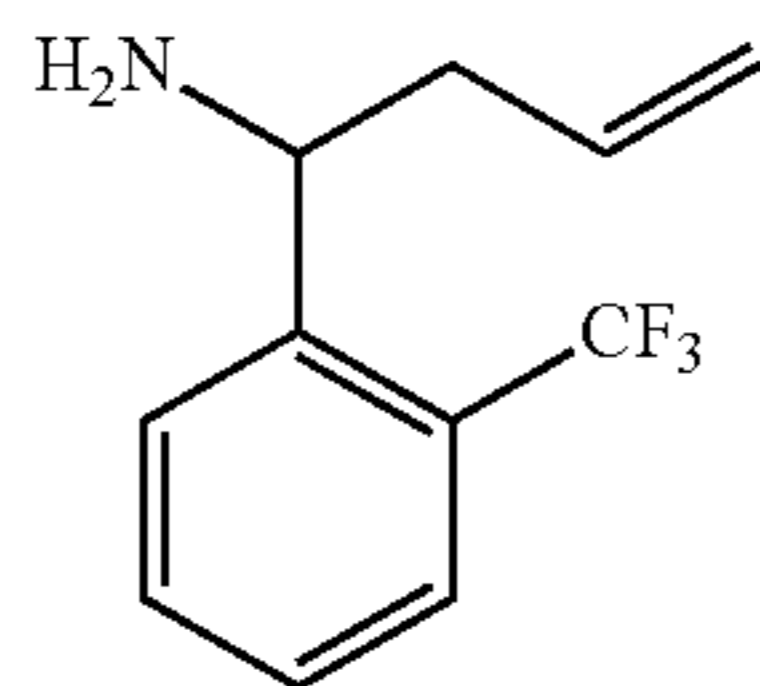
## Example 1

2-(4-(2-Hydroxypropan-2-yl)phenyl)-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol



## Intermediate 1A:

1-(2-(Trifluoromethyl)phenyl)but-3-en-1-amine



Aqueous ammonium hydroxide (28-30% by weight) (15.5 mL, 399 mmol) was added to a solution of 2-(trifluoromethyl)benzaldehyde (2.0 g, 11.49 mmol) in ethanol (46 mL) at room temperature under N<sub>2</sub>, generating a yellow color (no exotherm). Stirring was continued for 55 minutes at room temperature. The reaction flask was immersed in a 0° C. ice bath. Next, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.32 g, 13.79 mmol) was slowly added, causing turbidity and a lightening of the initially yellow color. The ice bath was removed, the mixture was allowed to return to room temperature and stirring was continued for 16 hrs. The reaction mixture went from a pale yellow solution to a cloudy white solution over the course of the reaction.

LCMS after 16 h indicated that the reaction was almost complete. Additional ammonium hydroxide was added (4.0 eq, 4.0 mL) and stirring was continued for 30 minutes. Additional 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was also added (0.39 g, 0.20 eq) and stirring was continued for 2.5 h. The reaction mixture was concentrated under vacuum. EtOAc (100 mL) and water (50 mL) were added. The layers were separated, the aqueous layer was extracted with EtOAc, the combined EtOAc layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 3.38 g of a pale yellow oil.

The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and 3 drops of NH<sub>4</sub>OH were added. After 1 minute, the precipitated white solid was removed by filtration. More of the white solid appeared in the filtrate, and was again removed by filtration. Ammonium hydroxide was added to the filtrate (3 drops) and the crude product was then flash-chromatographed on silica gel (Teledyne-Isco REDISEP® Rf 80 g column), eluting with 5-100% EtOAc in hexanes, 27 minute gradient, to yield 1.70 g of a light yellow oil (77%). LCMS:

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m/z 216.1 (M+H), 431.1 (2M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.87 (d, J=7.8 Hz, 1H), 7.76-7.57 (m, 2H), 7.52-7.21 (m, 1H), 5.77 (ddt, J=17.1, 10.2, 7.1 Hz, 1H), 5.17-4.86 (m, 2H), 4.32-4.05 (m, 1H), 3.92 (s, 1H), 2.42-2.13 (m, 2H).

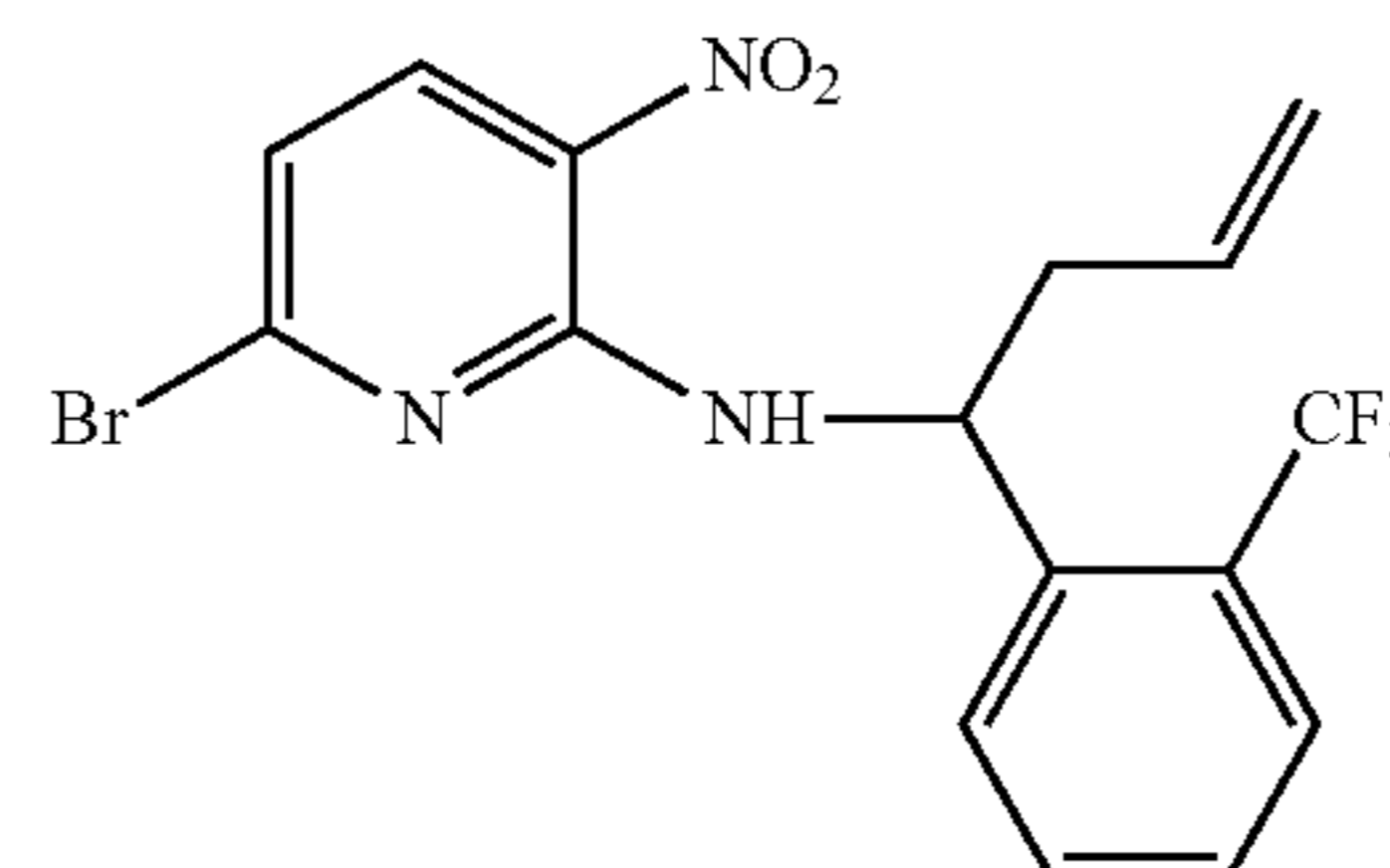
Intermediate 1B: 6-Bromo-3-nitro-N-(1-(2-(trifluoromethyl)phenyl)but-3-en-1-yl)pyridin-2-amine

(1)

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(1B)

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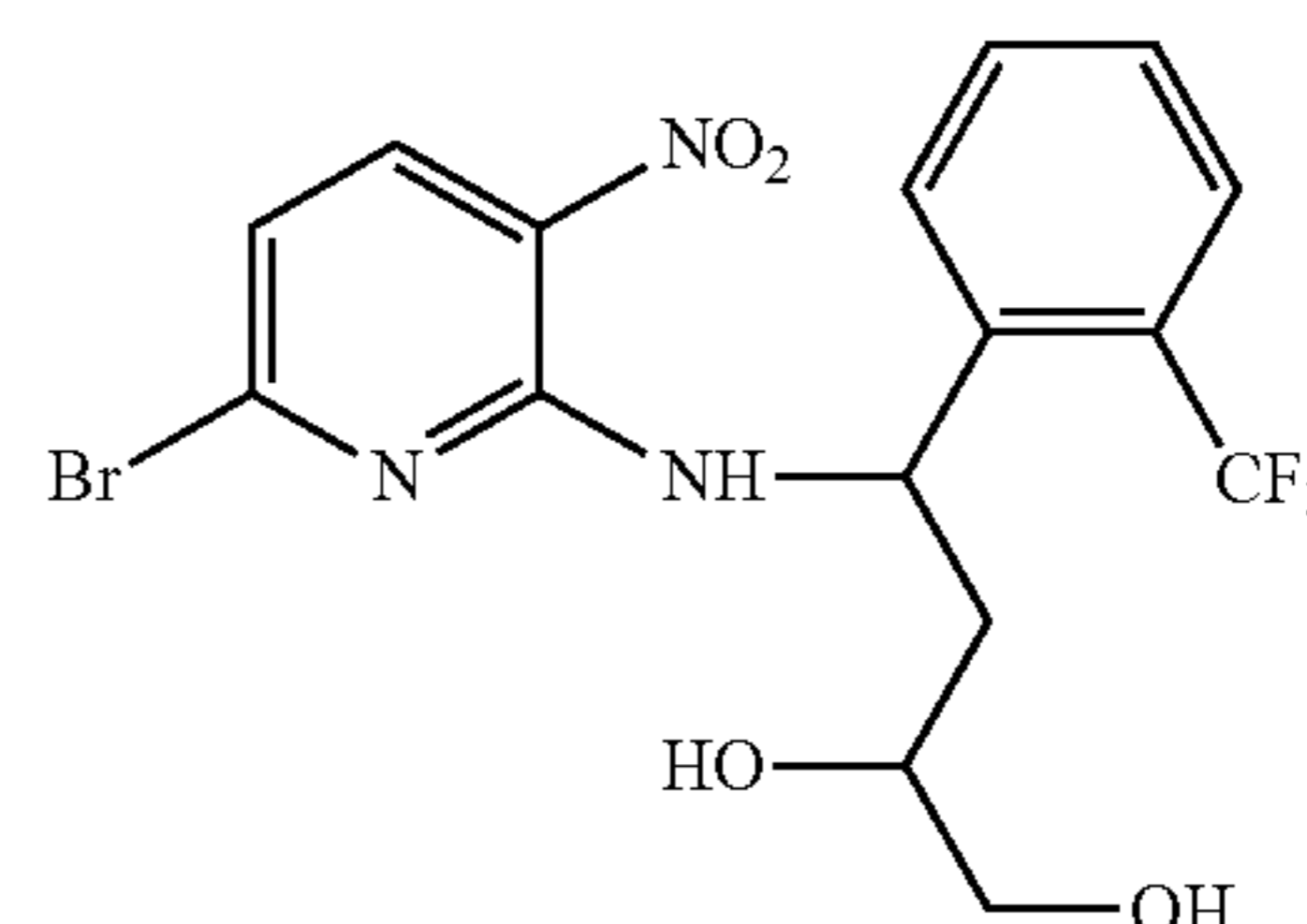
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Sodium carbonate (1.75 g, 16.48 mmol) was added to a stirred solution of Intermediate 1A (1-(2-(trifluoromethyl)phenyl)but-3-en-1-amine) (1.50 g, 6.97 mmol) and 2,6-dibromo-3-nitropyridine (1.8 g, 6.34 mmol) in ethanol (63.4 mL) at room temperature in a nitrogen flushed sealed vial. The resulting mixture was stirred at 60° C. for 16 h. Additional Intermediate 1A was added (0.20 g, 0.15 eq), and heating at 60° C. was continued for 3 h and 10 minutes. The reaction temperature was increased to 75° C., and stirring was continued for 20 h at which point the reaction was judged to be complete LCMS (m/z 416.0 and 418.0, M+H for desired product). Ethanol was removed under vacuum. EtOAc (100 mL) and water (50 mL) were added. The layers were separated, the EtOAc layer was washed with 50 mL of water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 2.85 g of a yellow viscous oil that began to solidify. Flash chromatography on silica gel (Teledyne-Isco REDISEP® Rf 80 g column), eluting with 0-40% EtOAc in hexanes, 28-minute gradient with an initial 5-minute hold on 100% hexanes, yielded 2.04 g of a neon yellow solid. LCMS, chromatographed product: m/z 417.9.0 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.78 (d, J=6.7 Hz, 1H), 8.28 (d, J=8.4 Hz, 1H), 7.81 (s, 1H), 7.73 (d, J=7.5 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.53-7.38 (m, 1H), 6.94 (d, J=8.6 Hz, 1H), 5.84 (ddt, J=17.1, 10.1, 7.0 Hz, 1H), 5.57 (t, J=10.1 Hz, 1H), 5.26 (dd, J=17.1, 1.9 Hz, 1H), 5.20-5.06 (m, 1H), 2.86-2.72 (m, 1H), 2.64-2.54 (m, 1H).

Intermediate 1C: 4-((6-Bromo-3-nitropyridin-2-yl)amino)-4-(2-(trifluoromethyl)phenyl)butane-1,2-diol

(1C)

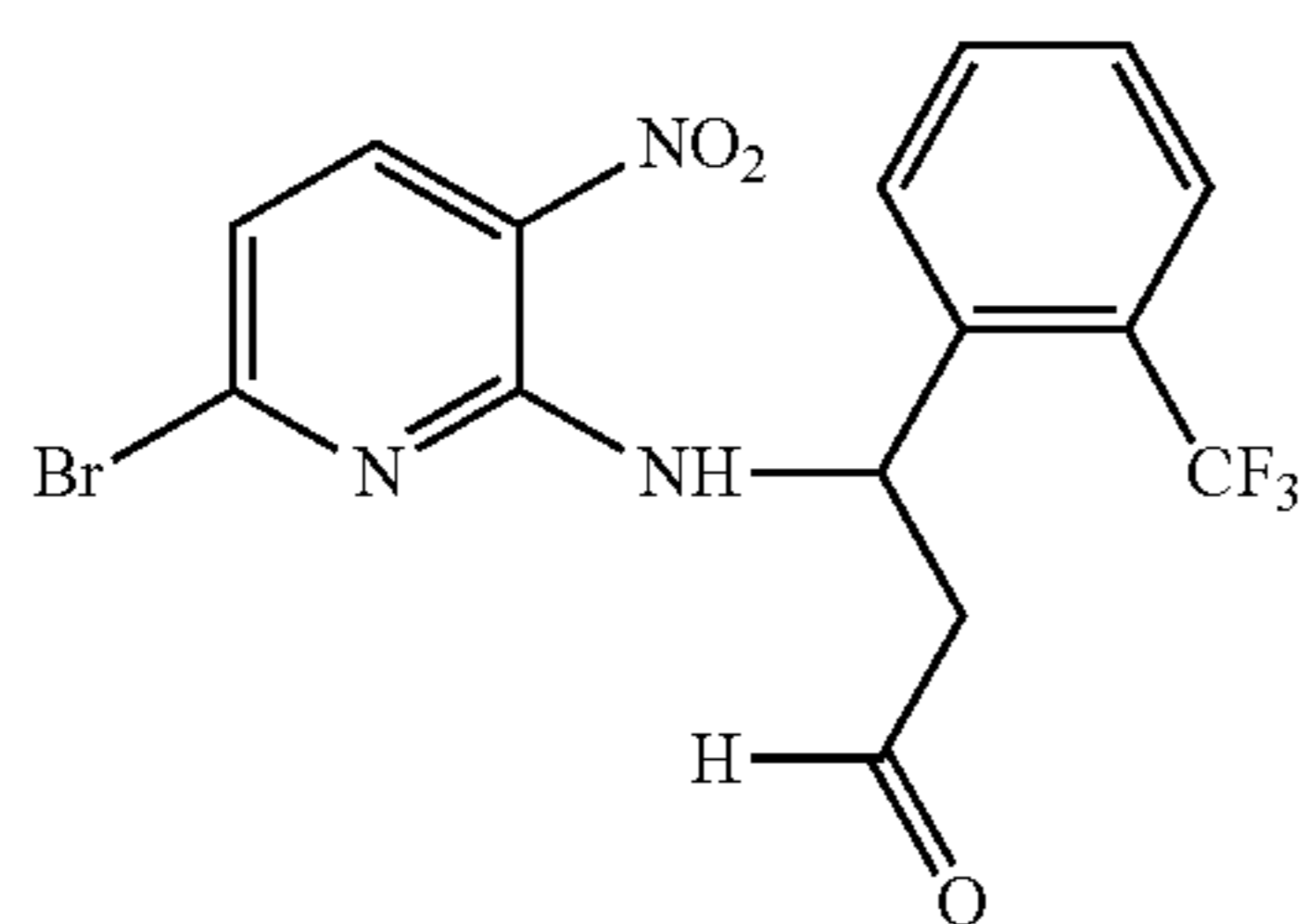




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NMO (50% aq solution) (2.0 mL, 9.69 mmol) and osmium tetroxide (2.5 wt. % in t-BuOH) (1.8 mL, 0.140 mmol) was added to a stirred solution of Intermediate 1B (6-bromo-3-nitro-N-(1-(2-(trifluoromethyl)phenyl)but-3-en-1-yl)pyridin-2-amine) (2.02 g, 4.84 mmol) in THF (28 mL) at 0° C. under N<sub>2</sub>. The ice bath was removed and stirring was continued for 5.5 hrs. The reaction mixture gradually turned from yellow to orange. LCMS at this point indicated a complete reaction (m/z 449.9 w/Br-pattern, M+H for desired product). EtOAc (100 mL) and water (50 mL) were added. The layers were separated, the aqueous layer was extracted with 50 mL of EtOAc after adding brine, the combined EtOAc layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 2.05 g of an orange somewhat sticky solid (94%). LCMS: m/z 449.9. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.84 (d, J=6.5 Hz, 0.50 H), 9.51 (d, J=4.5 Hz, 1H), 8.27 (dd, J=8.6, 0.7 Hz, 0.50 H), 7.79-7.66 (m, 2H), 7.62-7.54 (m, 1H), 7.51-7.35 (m, 1H), 6.88 (dd, J=8.6, 1.1 Hz, 1H), 5.85-5.71 (m, 1H), 5.49-5.35 (m, 1H), 5.26 (d, J=3.7 Hz, 1H), 5.15 (d, J=4.6 Hz, 1H), 3.39-3.28 (m, 1H), 3.24-3.13 (m, 1H), 2.08-1.99 (m, 1H), 1.92-1.72 (m, 1H).

Intermediate 1D: 3-((6-Bromo-3-nitropyridin-2-yl)amino)-3-(2-(trifluoromethyl)phenyl)propanal

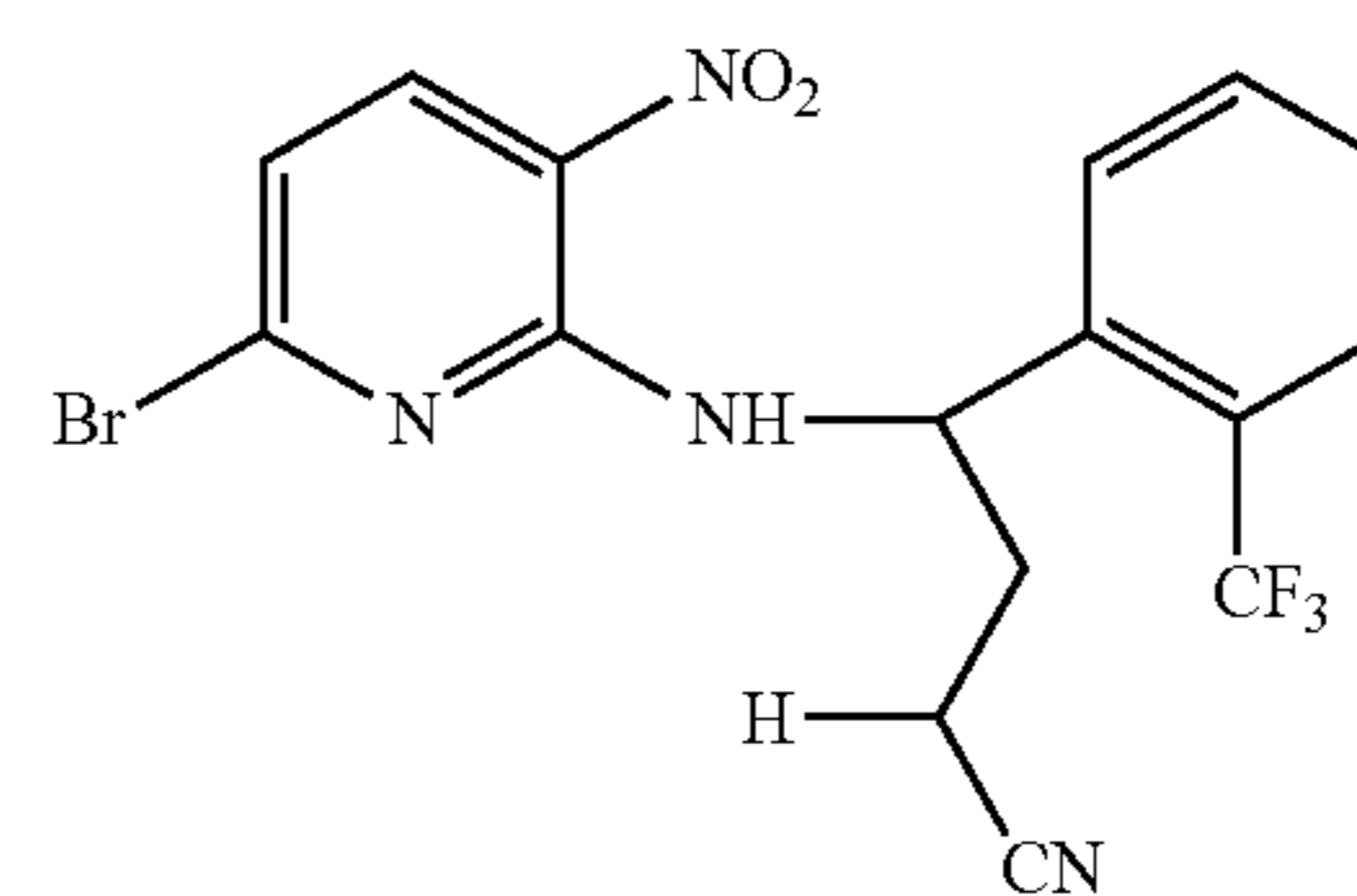


Sodium periodate (3.90 g, 18.23 mmol) was added to a stirred partial solution of Intermediate 1C (4-((6-bromo-3-nitropyridin-2-yl)amino)-4-(2-(trifluoromethyl)phenyl)butane-1,2-diol) (2.05 g, 4.56 mmol) in THF (26.3 mL) and water (25.5 mL) at room temperature under N<sub>2</sub>. All but a small amount of sodium periodate dissolved, followed by yellow precipitation and a slight exotherm. The suspension was stirred for 2 hrs. EtOAc (100 mL) and water (50 mL) were added. The layers were separated, the aqueous layer was extracted with 25 mL of EtOAc, and the combined EtOAc layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 1.83 g of an orange viscous oil. The crude product was dissolved in THF (26.3 mL). Water (25.5 mL) was added, followed by 1.0 eq of sodium periodate (0.975 g). Stirring was continued for 1.5 hr. LCMS after 50 minutes indicated no change. The above workup was repeated. Yield: 1.80 g of a viscous orange oil (94%). LCMS: m/z 420.0 w/Br-pattern (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.69 (d, J=1.0 Hz, 1H), 8.93 (d,

## 42

J=7.0 Hz, 1H), 8.29 (d, J=8.6 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.73 (d, J=7.8 Hz, 1H), 7.65 (t, J=7.3 Hz, 1H), 7.48 (dd, J=7.9, 6.2 Hz, 1H), 6.96 (d, J=8.6 Hz, 1H), 6.06 (t, J=7.2 Hz, 1H), 3.55 (ddd, J=18.2, 10.3, 1.5 Hz, 1H), 2.86 (dd, J=18.1, 3.1 Hz, 1H).

Intermediate 1E: 4-((6-Bromo-3-nitropyridin-2-yl)amino)-2-hydroxy-4-(2-(trifluoromethyl)phenyl)butanenitrile



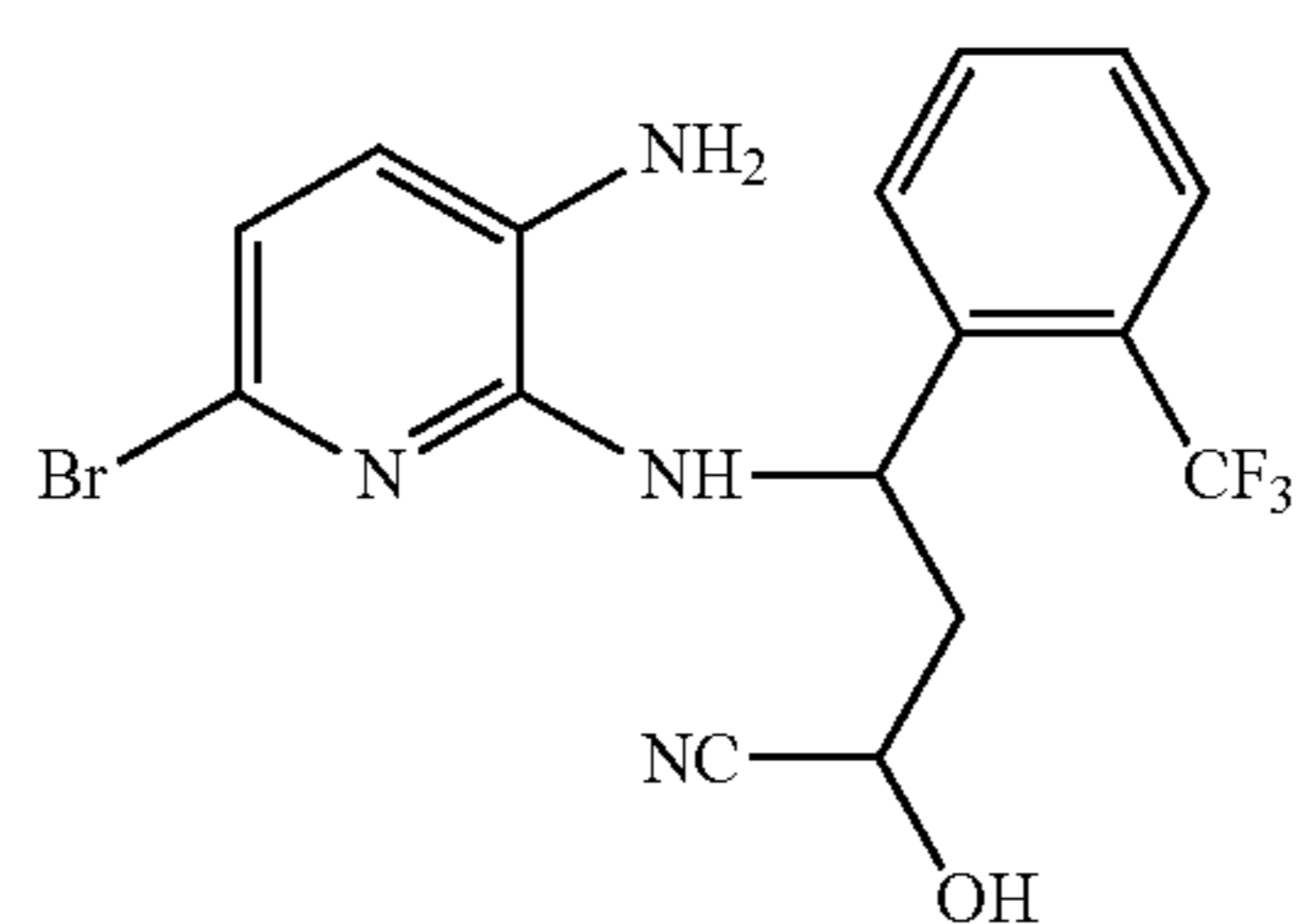
(1E)

A cloudy solution of Intermediate 1D (3-((6-bromo-3-nitropyridin-2-yl)amino)-3-(2-(trifluoromethyl)phenyl)propanal) (1.79 g, 4.28 mmol), acetone cyanohydrin (2.0 mL, 21.40 mmol), and triethylamine (7.76 μL, 0.056 mmol) in dichloromethane (9 mL) was stirred at room temperature under N<sub>2</sub> for 30 minutes. Additional triethylamine (8 μL, 0.056 mmol) was added, and stirring was continued for 45 minutes, followed by a second addition of triethylamine (8 μL, 0.056 mmol) and stirring was continued for 16 h. LCMS was obtained after 16 h at which time the reaction was judged to be incomplete. Additional triethylamine (8 μL, 0.056 mmol) was added, and stirring was continued for 2 h at which time the reaction was judged complete (LCMS after 1.5 h (m/z 445/447.0, M+H for desired product). The volatiles were removed under reduced pressure and EtOAc (100 mL) and water (25 mL) were added. The layers were separated and the aqueous layer was extracted with additional EtOAc (20 mL). The combined EtOAc layers were washed with water, brine, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to yield 1.8 g of a dark oil. The crude product was dissolved in a minimal amount of CH<sub>2</sub>Cl<sub>2</sub> and purified by flash chromatography on silica gel (Teledyne-Isco REDISEP® Rf 80 g column), eluting with 0-60% EtOAc in hexanes, 27 minute gradient. Yield: 1.49 g of a yellow oil/solid (78%). LCMS: m/z 446.9 w/Br-pattern (M+H). LCMS showed dual peaks (diastereomeric mixture). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.19 (d, J=7.0 Hz, 0.5H), 9.07 (d, J=7.1 Hz, 0.5H), 8.29 (d, J=2.2 Hz, 0.5H), 8.27 (d, J=2.2 Hz, 0.5H), 7.88 (d, J=7.8 Hz, 0.5H), 7.79 (d, J=7.9 Hz, 0.5H), 7.72 (d, J=7.8 Hz, 1H), 7.65 (td, J=7.3, 3.1 Hz, 0.5H), 7.52-7.43 (m, 0.5H), 6.94 (dd, J=8.5, 6.3 Hz, 0.5H), 6.75 (d, J=5.7 Hz, 0.5H), 6.71 (d, J=6.2 Hz, 0.5H), 5.89-5.79 (m, 1H), 4.77 (dt, J=8.4, 5.8 Hz, 0.5H), 4.72-4.59 (m, 0.5H), 2.75-2.57 (m, 0.5H), 2.22-2.04 (m, 0.5H).



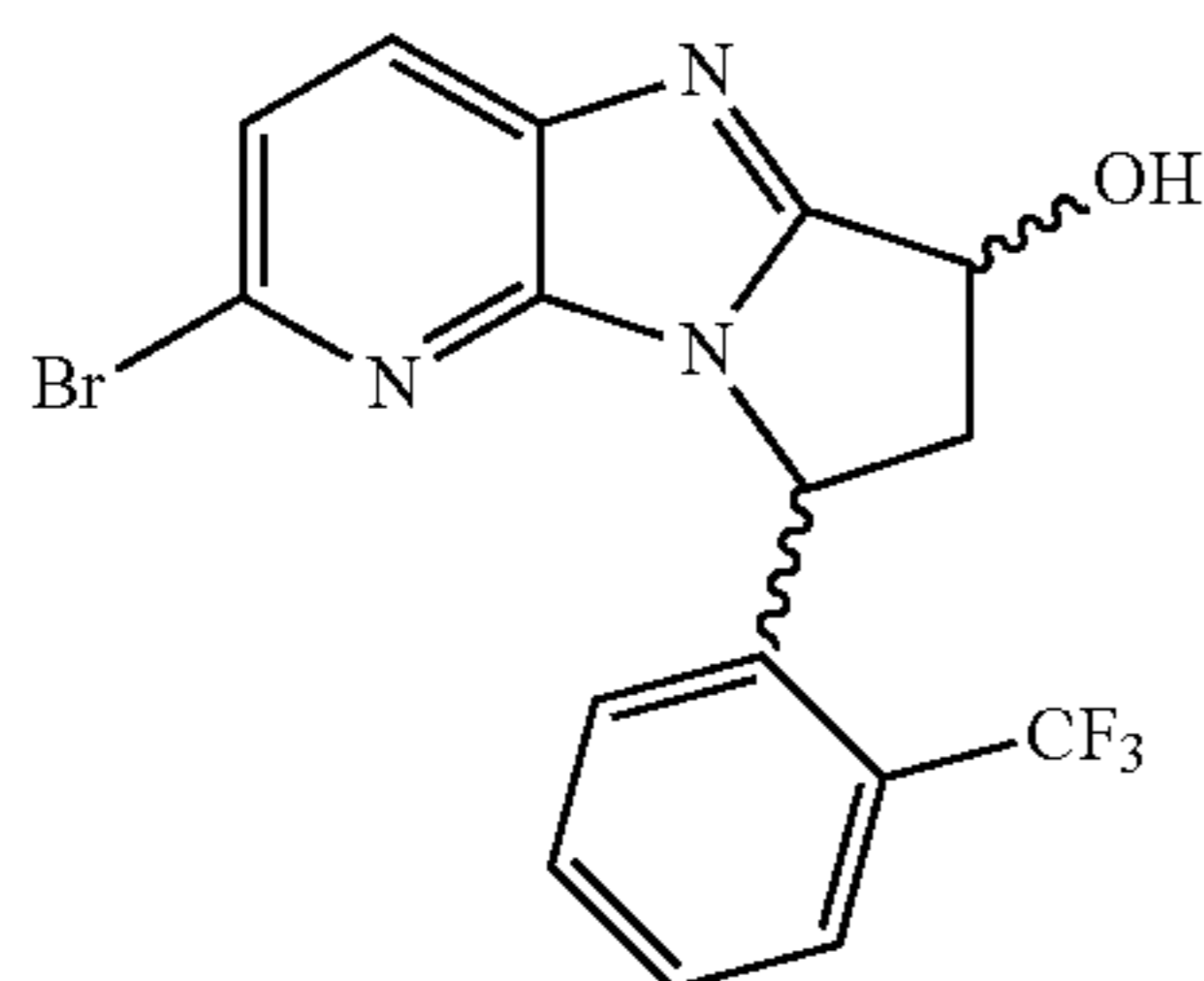
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Intermediate 1F: 4-((3-Amino-6-bromopyridin-2-yl)amino)-2-hydroxy-4-(2-(trifluoromethyl)phenyl)butanenitrile



A solution of ammonium chloride (1.62 g, 30.3 mmol) in water (3.4 mL) was added to a vigorously stirred solution of Intermediate 1E (4-((6-bromo-3-nitropyridin-2-yl)amino)-2-hydroxy-4-(2-(trifluoromethyl)phenyl)butanenitrile) (1.35 g, 3.03 mmol) in ethanol (13 mL) and THF (6.72 mL) at 0° C. followed by zinc (flakes) (1.98 g, 30.3 mmol). Stirring at 0° C. was continued for 20 minutes. LCMS after 5 minutes indicated a complete reaction (m/z 415.0/417.0, M+H for desired product). MgSO<sub>4</sub> was added (1.5 g) and stirring at 0° C. was continued for 1 more minute. The reaction mixture was then filtered through CELITE®, followed by several ethanol rinses. The filtrate was concentrated to dryness under reduced pressure. EtOAc and saturated aqueous NaHCO<sub>3</sub> were added. The layers were separated, the EtOAc layer was washed with saturated aqueous NaHCO<sub>3</sub> solution, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 1.12 g of an orange oily foam (89%). LCMS: m/z 415.0/417.0 (M+H). UPLC: 93.495-95.291% pure product (2 closely-spaced peaks, diastereomers). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.71-7.66 (m, 1H), 7.64-7.58 (m, 1H), 7.45-7.38 (m, 1H), 6.63 (d, J=2.1 Hz, 0.5H), 6.62-6.60 (m, 0.5H), 6.57-6.51 (m, 1H), 6.46 (d, J=5.3 Hz, 0.5H), 6.44 (d, J=5.4 Hz, 0.5H), 6.41 (s, 2H), 5.52 (q, J=8.4 Hz, 1H), 4.98 (d, J=10.8 Hz, 1H), 4.89-4.60 (m, 1H), 2.36-1.97 (m, 2H).

Intermediate 1G: 2-Bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol



A solution of Intermediate 1F, 4-((3-amino-6-bromopyridin-2-yl)amino)-2-hydroxy-4-(2-(trifluoromethyl)phenyl)butanenitrile (1.11 g, 2.67 mmol) in ethanol (27 mL) and sulfuric acid (0.4 mL, 6.68 mmol) was heated at 120° C. under N<sub>2</sub> for 1.5 hr. Additional sulfuric acid (0.4 mL, 6.68 mmol) was added, and heating at 120° C. was continued for 4 h, then left stirring at room temperature over the weekend.

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At this point the reaction was analyzed by LCMS and judged to be incomplete. Additional sulfuric acid was added (0.2 mL) and heating at 120° C. was continued for 7.5 h, at which point the reaction was judged complete (LCMS after 4 hrs./15 m (m/z 399.9 w/Br-pattern, M+H for desired product). Ethanol was removed under vacuum. Saturated aqueous NaHCO<sub>3</sub> solution was added, followed by a brief sonication. The precipitate was collected by filtration, rinsed with water, and dried under vacuum to yield 0.927 g of a pale tan solid (86%). LCMS: m/z 397.9 w/Br-pattern (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.09 (d, J=5.9 Hz, 0.5H), 8.06 (d, J=6.0 Hz, 0.5H), 7.90-7.81 (m, 1H), 7.66-7.52 (m, 2H), 7.46 (d, J=4.2 Hz, 0.5H), 7.44 (d, J=4.3 Hz, 0.5H), 7.07 (d, J=7.5 Hz, 0.5H), 6.91 (d, J=6.2 Hz, 0.5H), 6.21 (d, J=5.6 Hz, 0.5H), 6.15 (d, J=6.8 Hz, 0.5H), 6.06 (t, J=6.4 Hz, 0.5H), 5.92-5.82 (m, 0.5H), 5.32 (td, J=7.0, 4.2 Hz, 0.5H), 5.27-5.17 (m, 0.5H), 3.57-3.45 (m, 0.25H), 3.01-2.91 (m, 0.25H), 2.78 (dt, J=13.2, 6.6 Hz, 0.25H), 2.30-2.17 (m, 0.25H).

### Example 1

A suspension of Intermediate 1G, 2-bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (30.0 mg, 75 μmol) and (4-(2-hydroxypropan-2-yl)phenyl)boronic acid (16.3 mg, 90 μmol) in dioxane (753 μl) and tripotassium phosphate (2.0 M aq solution) (113 μl, 226 μmol) was degassed for several minutes with N<sub>2</sub>. While still degassing, 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (1.825 mg, 2.80 μmol) mmol) was added. The vial was sealed and heating at 90° C. for 1 h, at which point the reaction was analyzed by LCMS and judged incomplete. Additional boronic acid (7.0 mg, 0.52 eq), was added at room temperature, the reaction mixture was degassed, and additional 1,1'-bis(di-tert-butylphosphino) ferrocene palladium dichloride (1.8 mg, 2.80 μmol) was added. The vial was sealed, and heated at 90° C. with stirring for an additional 1 h. At this point the reaction was analyzed by LCMS and judged complete (m/z 454.1, M+H for desired product). The reaction mixture was allowed to cool to room temperature, the volatiles removed under reduced pressure and the reaction mixture was diluted with methanol at room temperature and filtered through a 13 mm syringe filter with a 0.45 Nylon membrane. The filtrate was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19×200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 20-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation. Yield: 25 mg as a mixture of four enantiomers. The material was further purified through chiral separation. Approximately 25 mg sample was resolved. The fractions ("Peak-1", "Peak-2", "Peak-3" and "Peak-4") were collected in methanol. The stereoisomeric purity of each fraction was estimated to be greater than 99.0% based on the prep-SFC chromatograms.

Preparative chromatographic conditions: Instrument: Waters SFC-100 MS. Column: Lux Cellulose 4 25×3 cm ID, 5 mm. Flow rate: 100 mL/min. Mobile phase: 70/30 CO<sub>2</sub>/methanol. Detector wavelength: 220 nm. Sample prep and inj. Volume: 1000 mL of 25 mg dissolved in 3.5 mL of methanol/acetonitrile.



Analytical chromatogram conditions: Instrument: Aurora analytical SFC. Column: Lux Cellulose 4 250x4.6 mm ID, 5 mM. Flow rate: 2.0 mL/min. Mobile phase: 70/30 CO<sub>2</sub>/methanol.

Yield of individual enantiomers (absolute stereochemistry undetermined):

Example 1, enantiomer 1 (first eluting peak) 3.9 mg (9.93%). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.10 (d, J=8.5 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.79 (d, J=8.5 Hz, 1H), 7.74 (d, J=8.5 Hz, 2H), 7.60-7.55 (m, 1H), 7.55-7.49 (m, 1H), 7.45 (d, J=8.2 Hz, 2H), 7.22 (d, J=7.6 Hz, 1H), 5.97-5.86 (m, 1H), 5.29 (br. s., 1H), 3.59-3.47 (m, 1H), 2.36-2.23 (m, 1H), 1.40 (s, 6H).

Example 1, enantiomer 2 (second eluting peak) 2.9 mg (7.05%). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.10 (d, J=8.5 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.79 (d, J=8.5 Hz, 1H), 7.74 (d, J=8.5 Hz, 2H), 7.60-7.55 (m, 1H), 7.55-7.49 (m, 1H), 7.45 (d, J=8.2 Hz, 2H), 7.22 (d, J=7.6 Hz, 1H), 5.97-5.86 (m, 1H), 5.29 (br. s., 1H), 3.59-3.47 (m, 1H), 2.36-2.23 (m, 1H), 1.40 (s, 6H).

Example 1, enantiomer 3 (third eluting peak) 3.5 mg (10.24%). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.11 (d, J=8.2

Hz, 1H), 7.89-7.83 (m, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.72 (d, J=8.2 Hz, 2H), 7.61-7.49 (m, 3H), 7.45 (d, J=8.5 Hz, 2H), 7.02 (d, J=6.4 Hz, 1H), 6.09 (t, J=6.6 Hz, 1H), 5.35 (br. s., 1H), 3.01-2.95 (m, 1H), 2.88-2.80 (m, 1H), 1.40 (s, 6H).

Example 1, enantiomer 4 (fourth eluting peak) 2.6 mg (7.38%). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.11 (d, J=8.2 Hz, 1H), 7.89-7.83 (m, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.72 (d, J=8.2 Hz, 2H), 7.61-7.49 (m, 3H), 7.45 (d, J=8.5 Hz, 2H), 7.02 (d, J=6.4 Hz, 1H), 6.09 (t, J=6.6 Hz, 1H), 5.35 (br. s., 1H), 3.01-2.95 (m, 1H), 2.88-2.80 (m, 1H), 1.40 (s, 6H).

The Examples in Table 1 below were prepared according to the general procedure described in Example 1 by substitution of 2-(trifluoromethyl)benzaldehyde with the appropriate commercially available aldehyde as described in the preparation of Intermediate 1A, and substitution of (4-(2-hydroxypropan-2-yl)phenyl)boronic acid with the appropriate boronic acid or boronic ester as described in last step of the preparation of Example 1. Diastereomeric mixtures are designated as 'DM'. In cases where enantiomers were isolated the analytical data for each is included and designated as 'e1', 'e2', 'e3', and 'e4'.

TABLE 1

| Ex. No. | Structure | MS (M + 1) | HPLC Ret. Time (min) | HPLC Method |
|---------|-----------|------------|----------------------|-------------|
| 2       |           | 470.29(e1) | 1.75(e1)             | B(e1)       |
|         |           | 470.22(e2) | 1.61(e2)             | A(e2)       |
|         |           | 470.26(e3) | 1.72(e3)             | B(e3)       |
|         |           | 470.24(e4) | 1.60(e4)             | A(e4)       |
| 3       |           | 472.24(e1) | 1.69(e1)             | B(e1)       |
|         |           | 471.18(e2) | 1.67(e2)             | B(e2)       |
|         |           | 471.19(e3) | 1.68(e3)             | B(e3)       |
|         |           | 471.18(e4) | 1.67(e4)             | B(e4)       |
| 4       |           | 414.20(DM) | 1.44(DM)             | A(DM)       |
| 5       |           | 415.98(DM) | 1.49(DM)             | A(DM)       |



TABLE 1-continued

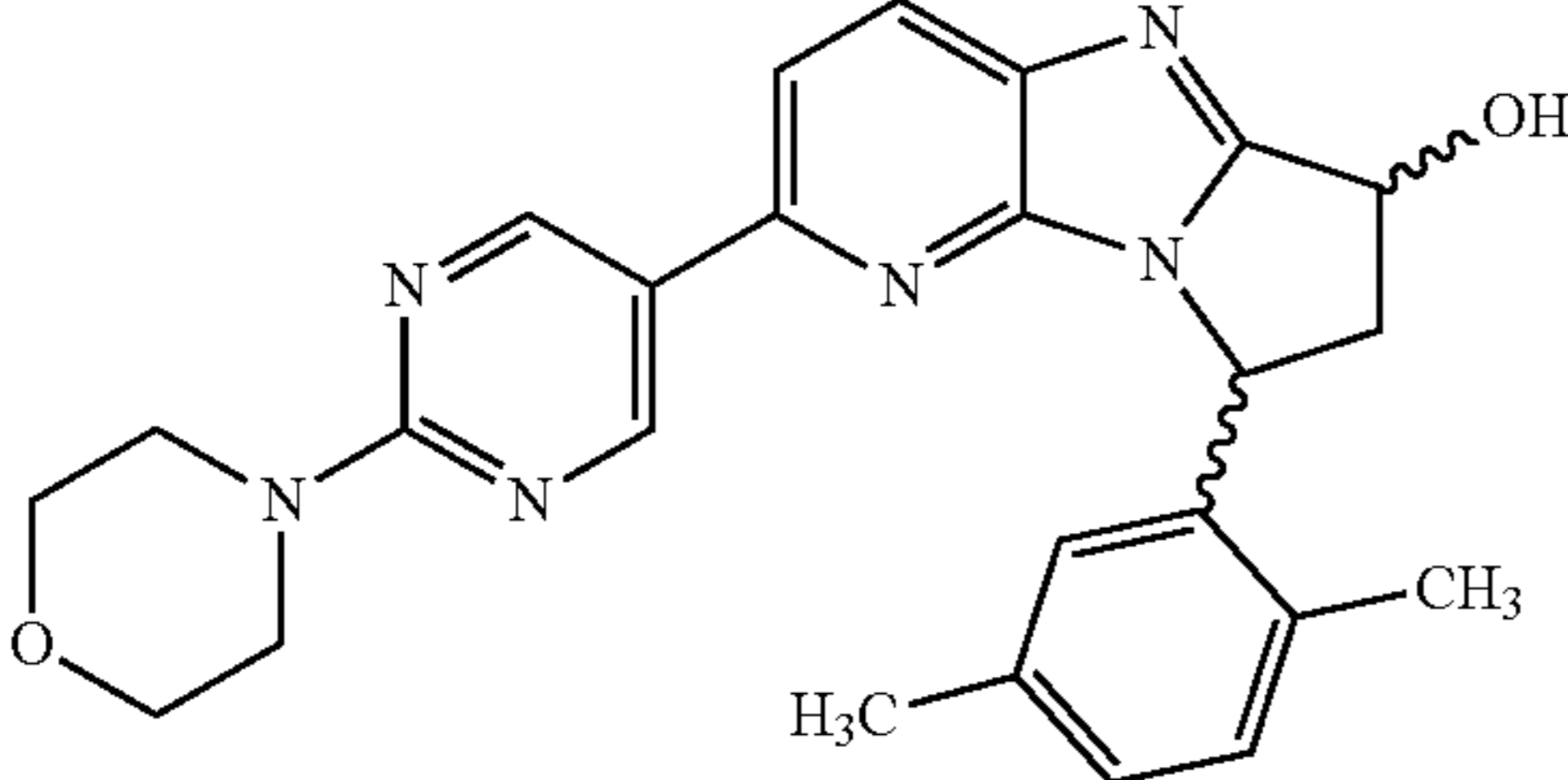
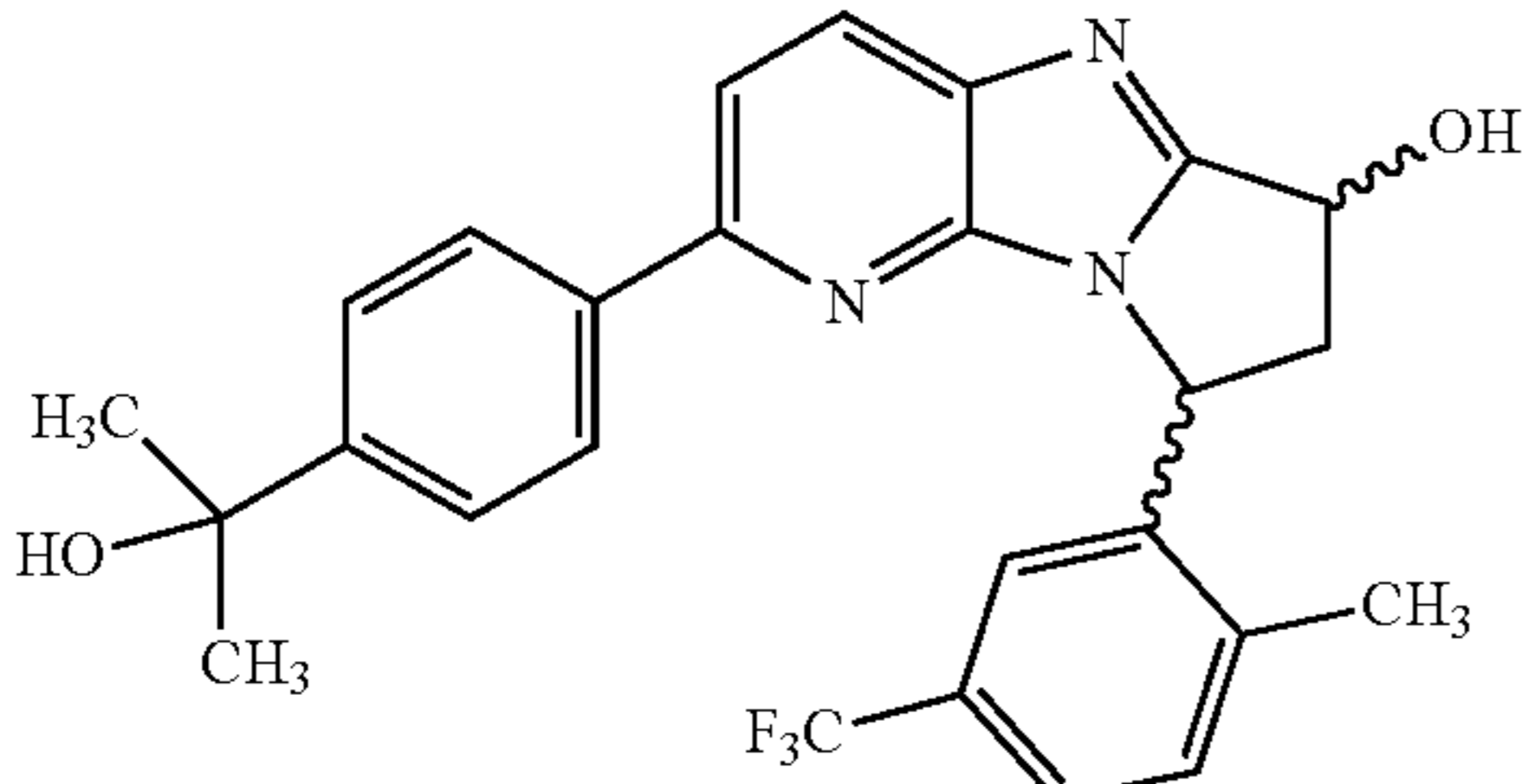
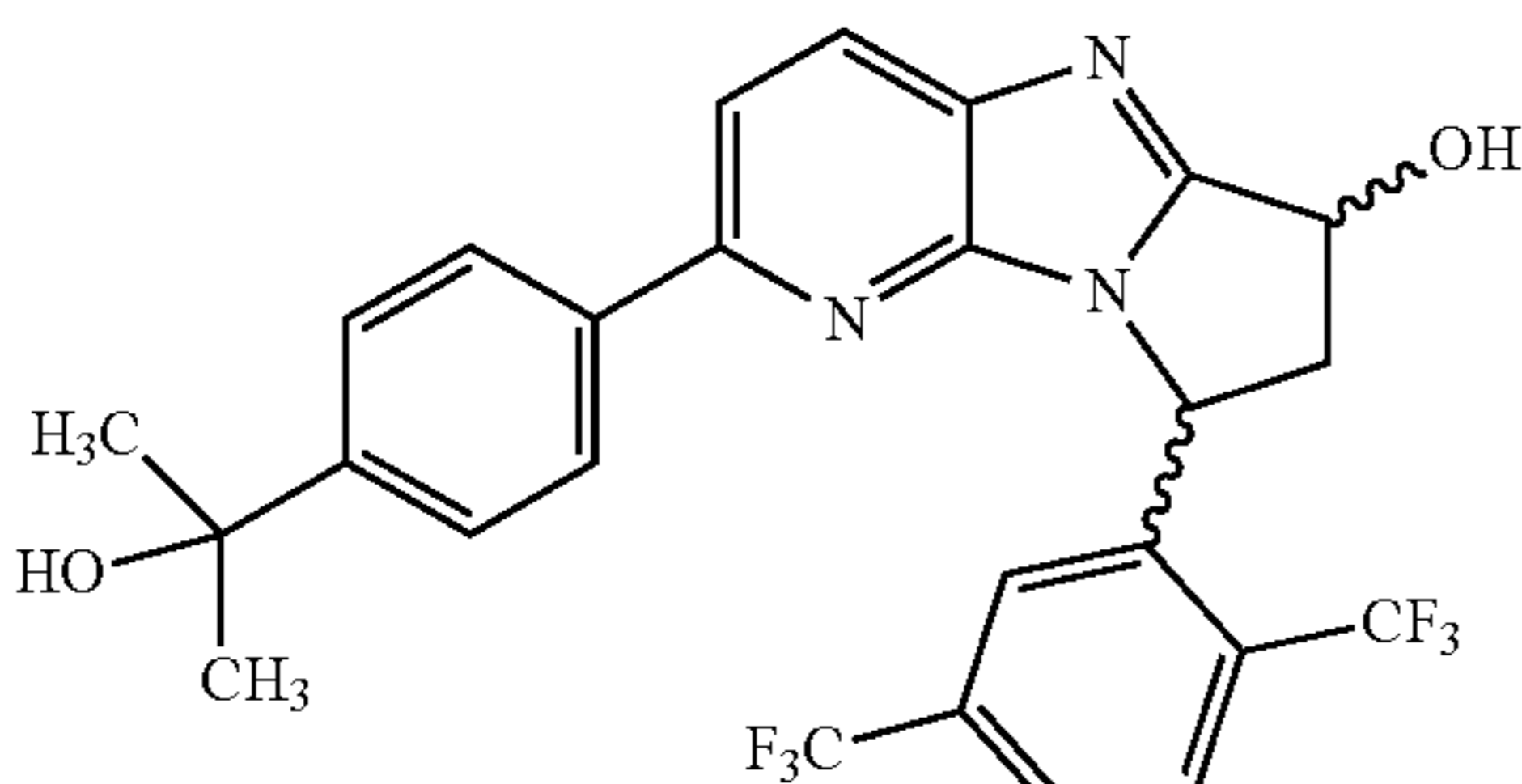
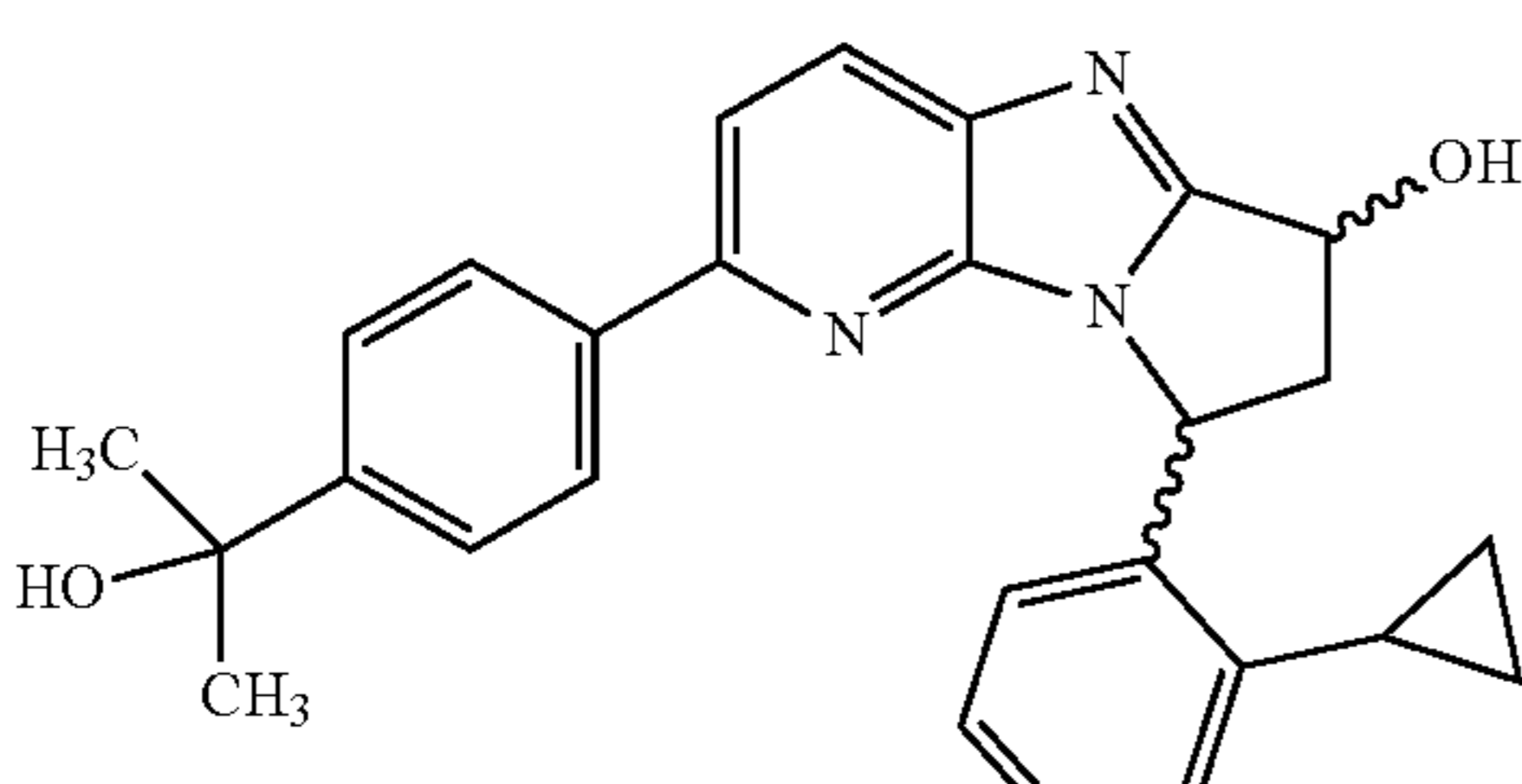
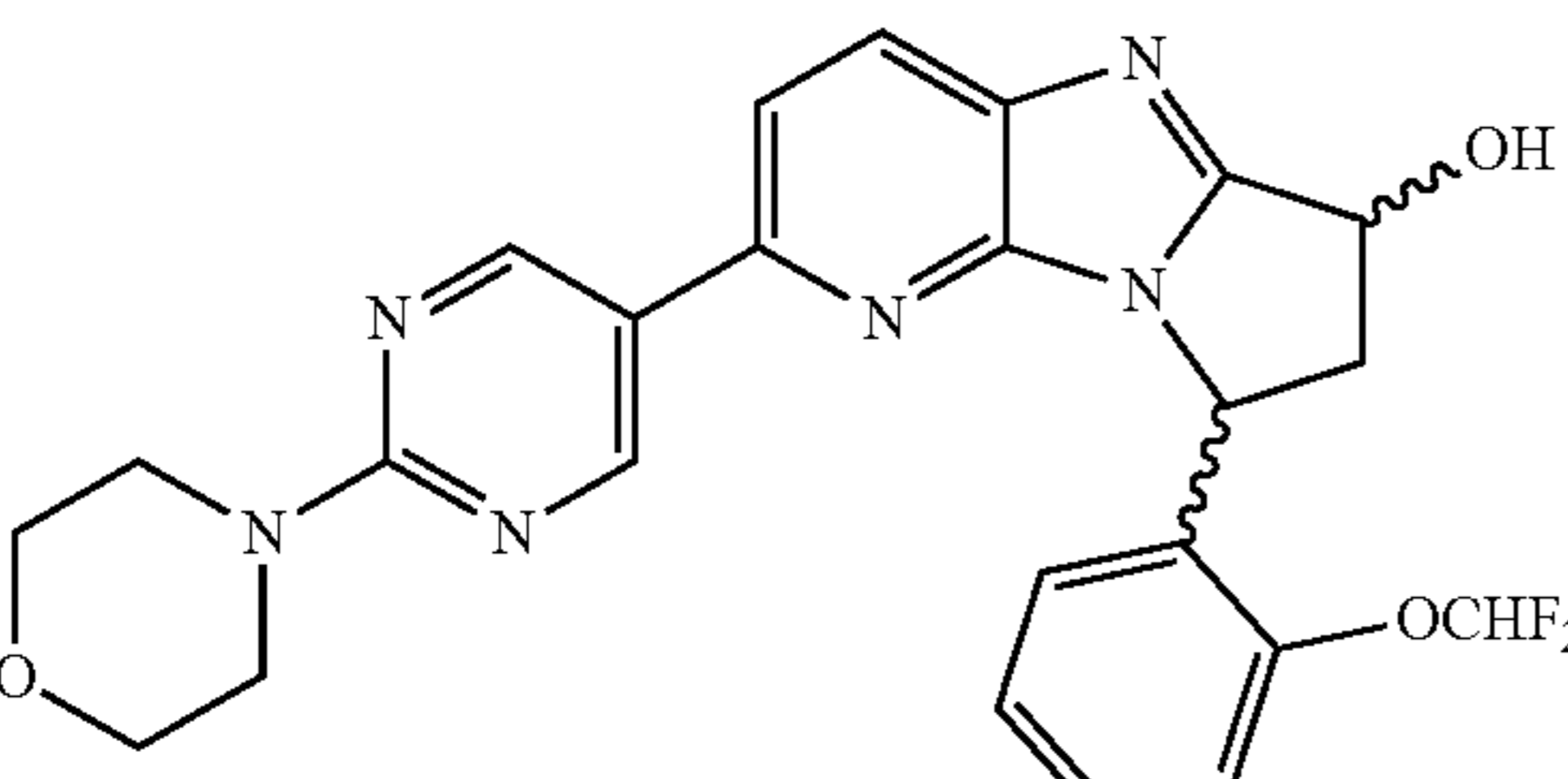
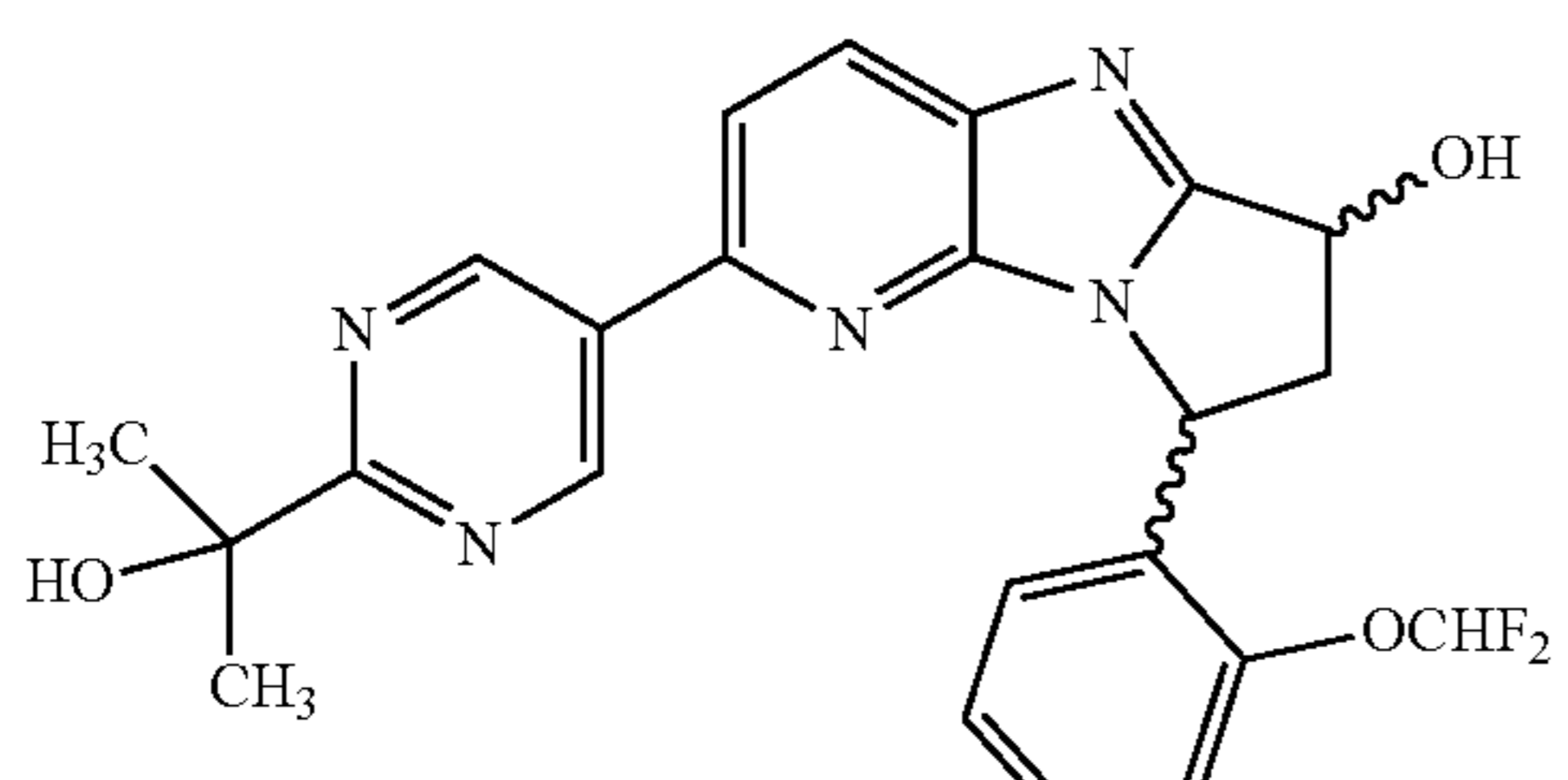
| Ex. No. | Structure   | MS (M + 1)   | HPLC Ret. Time (min)                         | HPLC Method                      |
|---------|---|--|--|----------------------------------|
| 6       |    | 443.05(DM)   | 1.42(DM)                                     | A(DM)                            |
| 7       |   | 468.11(DM)   | 1.65(DM)                                     | A(DM)                            |
| 8       |  | 522.28(DM)   | 1.77(DM)                                     | A(DM)                            |
| 9       |  | 425.92(e1)<br>426.25(e2)<br>425.96(e3)<br>425.92(e4) | 1.66(e1)<br>1.54(e2)<br>1.67(e3)<br>1.66(e4) | B(e1)<br>A(e2)<br>B(e3)<br>B(e4) |
| 10      |  | 481.05(DM)   | 1.37(DM)                                     | A(DM)                            |
| 11      |  | 454.20(e1)<br>454.15(e4)                             | 1.44(e1)<br>1.43(e4)                         | B(e1)<br>B(e4)                   |

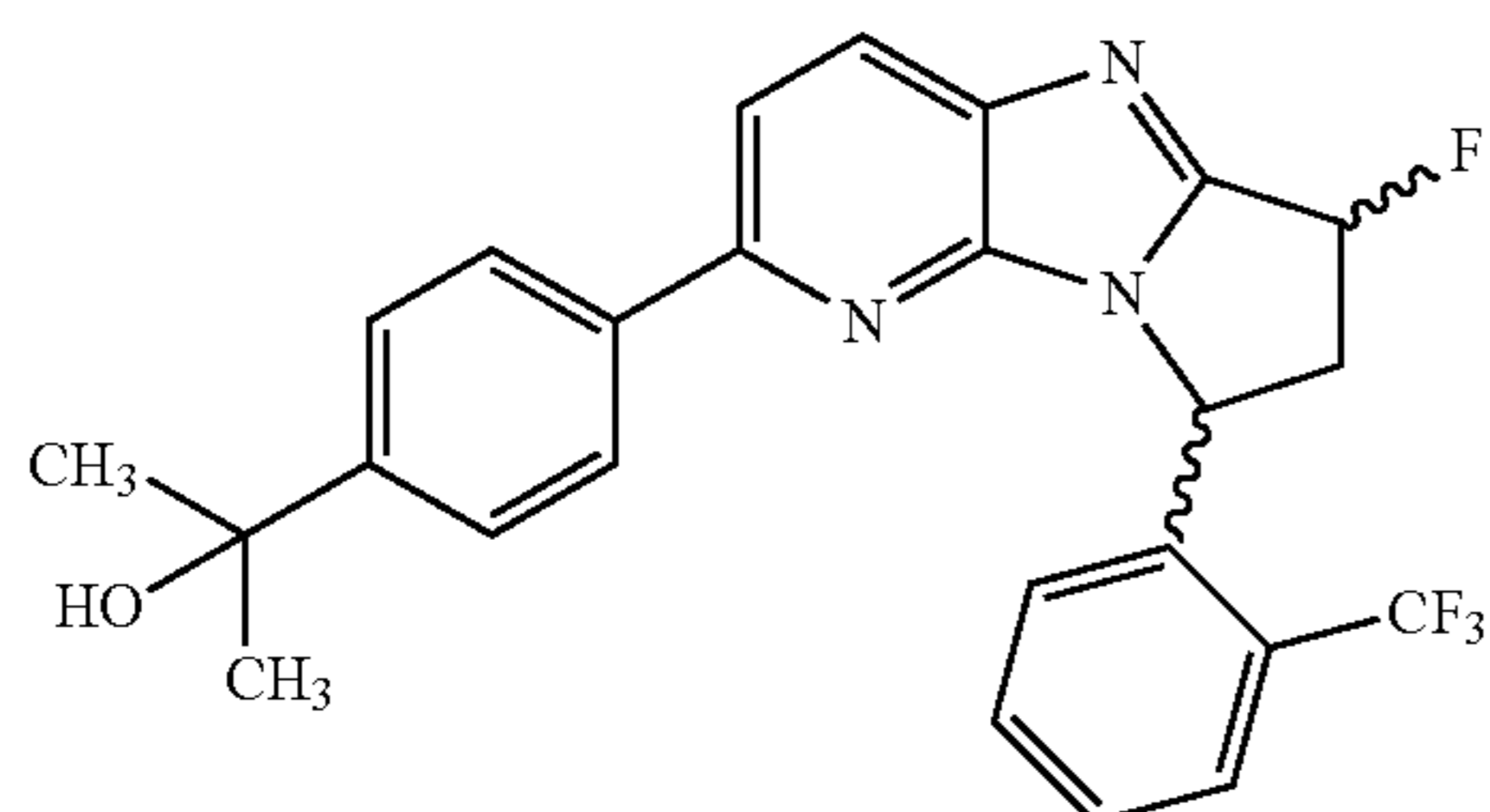


TABLE 1-continued

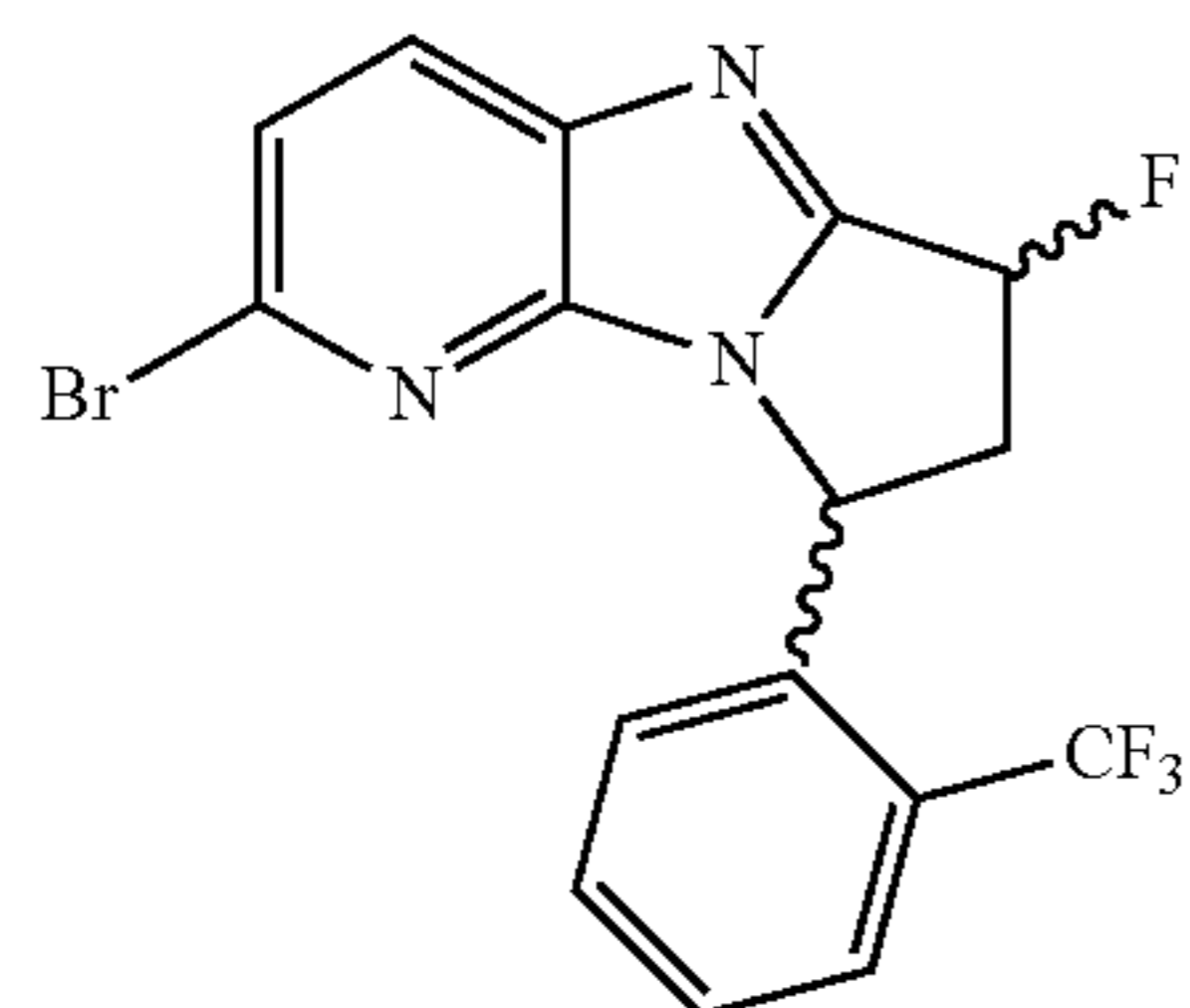
| Ex. No. | Structure | MS (M + 1) | HPLC Ret. Time (min) | HPLC Method |
|---------|-----------|------------|----------------------|-------------|
| 12      |           | 415.89(e2) | 1.45(e2)             | B(e2)       |
|         |           | 415.94(e3) | 1.57(e3)             | B(e3)       |
|         |           | 415.95(e4) | 1.33(e4)             | A(e4)       |
| 13      |           | 472.11(e1) | 1.75(e1)             | B(e1)       |
|         |           | 472.04(e2) | 1.65(e2)             | B(e2)       |
|         |           | 472.02(e3) | 1.60(e3)             | A(e3)       |
|         |           | 472.05(e4) | 1.73(e4)             | B(e4)       |

## Example 14

2-(4-(6-Fluoro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol



Intermediate 14A: 2-Bromo-6-fluoro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine



Diethylaminosulfur trifluoride (DAST) (0.060 mL, 0.452 mmol) was added dropwise to a suspension of 2-bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (0.10 g, 0.251 mmol) in

acetonitrile (2.51 mL) at 0° C. under N<sub>2</sub>. A brown-orange solution formed immediately. Stirring at 0° C. was continued for 45 minutes. The reaction was analyzed by LCMS after 25 min and judged complete (m/z 399.9 w/Br-pattern, M+H for desired product). While still at 0° C., the reaction mixture was diluted with EtOAc and saturated aqueous NaHCO<sub>3</sub> solution was slowly added. The layers were separated, the EtOAc layer was washed 2× with saturated aqueous NaHCO<sub>3</sub> solution, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 0.11 g of an orange solid. LCMS: m/z 401.9 w/Br-pattern (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.22 (d, J=8.6 Hz, 0.5H), 8.19 (d, J=8.6 Hz, 0.5H), 7.89 (d, J=2.4 Hz, 0.5H), 7.88-7.85 (m, 0.5H), 7.64-7.58 (m, 2H), 7.56 (d, J=8.4 Hz, 0.5H), 7.53 (d, J=8.4 Hz, 0.5H), 7.03 (d, J=6.4 Hz, 0.5H), 6.83 (d, J=6.1 Hz, 0.5H), 6.44 (dd, J=6.7, 2.3 Hz, 0.25H), 6.33-6.26 (m, 0.25H), 6.21-6.12 (m, 0.25H), 6.05 (br. s., 0.25H), 3.80-3.61 (m, 0.5H), 3.44-3.34 (m, 0.5H), 3.08-2.89 (m, 0.5H), 2.66-2.56 (m, 0.5H). The product was used as is for the next step without further purification.

## Example 14

A stirred solution of Intermediate 14A, 2-bromo-6-fluoro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (45 mg, 0.112 mmol) and (4-(2-hydroxypropan-2-yl)phenyl)boronic acid (26 mg, 0.146 mmol) in dioxane (1.1 mL) and tripotassium phosphate (2.0 M aq solution) (169 μL, 0.337 mmol) was degassed for several minutes with N<sub>2</sub>. While still degassing, 1,1'-bis(di-tert-butylphosphino) ferrocene palladium dichloride (7.30 mg, 0.0112 mmol) was added. The vial was sealed and heating at 90° C. for 70 minutes, at which point the reaction mixture was analyzed by LCMS and judged complete (m/z 456.0, M+H for desired product). The volatiles were removed under reduced pressure and the reaction mixture was diluted with methanol and filtered at room temperature through a 13 mm syringe filter with a 0.45 μNylon membrane. The filtrate was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19×200 mm, 5-μm particles; Mobile Phase A: 5:95



acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

The material was further purified through chiral separation. 15.5 mg sample was resolved. The fractions ("Peak-1", "Peak-2", "Peak-3", and "Peak-4") were collected in MeOH. The stereoisomeric purity of the fractions was estimated to be greater than 95% based on the prep-SFC chromatograms. Preparative Chromatographic Conditions: Instrument: Berger Prep SFC MGII (LVL-L4021 Lab). Column: Chiral OD 25x3 cm, 5 μm. Flow rate: 85.0 mL/min. Mobile Phase: 85/15 CO<sub>2</sub>/MeOH. Detector Wavelength: 220 nm. Sample Prep and Inj. Volume: 500 μL of 15.5 mg dissolved in 2.5 mL MeOH.

Analytical Chromatographic Conditions: Instrument: Aurora analytical SFC Instrument: Aurora analytical SFC (LVL-L4021 Lab). Instrument: Aurora analytical SFC Column: Chiral OD 250x4.6 mm ID, 5 μm. Flow rate: 2.0 mL/min. Mobile Phase: 85/15 CO<sub>2</sub>/MeOH. Separations were done on parallel SFC system.

Yield of individual enantiomers (absolute stereochemistry undetermined):

3.9 mg (9.93%), enantiomer 1, first eluting peak. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.23 (d, J=8.5 Hz, 1H), 7.91-7.89 (m, 1H), 7.87 (d, J=8.8 Hz, 1H), 7.73 (d, J=8.2 Hz, 2H), 7.62-7.55 (m, 2H), 7.46 (d, J=8.2 Hz, 2H), 7.13 (d, J=5.2 Hz, 1H), 6.46 (d, J=5.3 Hz, 1H), 6.35 (d, J=5.8 Hz, 1H), 6.18 (t, J=6.5 Hz, 1H), 3.48-3.29 (m, 1H), 3.13-2.94 (s, 6H).

2.9 mg (7.05%), enantiomer 2, second eluting peak. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.23 (d, J=8.5 Hz, 1H), 7.91-7.89 (m, 1H), 7.87 (d, J=8.8 Hz, 1H), 7.73 (d, J=8.2 Hz, 2H), 7.62-7.55 (m, 2H), 7.46 (d, J=8.2 Hz, 2H), 7.13 (d, J=5.2 Hz, 1H), 6.46 (d, J=5.3 Hz, 1H), 6.35 (d, J=5.8 Hz, 1H), 6.18 (t, J=6.5 Hz, 1H), 3.48-3.29 (m, 1H), 3.13-2.94 (m, 1H), 1.40 (s, 6H).

3.5 mg (10.24%), enantiomer 3, third eluting peak. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.26 (d, J=8.5 Hz, 1H), 7.90 (d, J=8.8 Hz, 1H), 7.89-7.86 (m, 1H), 7.82 (d, J=8.2 Hz, 2H), 7.62-7.52 (m, 2H), 7.49 (d, J=8.2 Hz, 2H), 6.92 (d, J=7.6 Hz, 1H), 6.30 (d, J=6.4 Hz, 1H), 6.18 (d, J=6.2 Hz, 1H), 6.09 (br. s., 1H), 3.86-3.62 (m, 1H), 2.74-2.60 (m, 1H), 1.41 (s, 6H).

2.6 mg (7.38%), enantiomer 4, fourth eluting peak. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.26 (d, J=8.5 Hz, 1H), 7.90 (d, J=8.8 Hz, 1H), 7.89-7.86 (m, 1H), 7.82 (d, J=8.2 Hz, 2H), 7.62-7.52 (m, 2H), 7.49 (d, J=8.2 Hz, 2H), 6.92 (d, J=7.6 Hz, 1H), 6.30 (d, J=6.4 Hz, 1H), 6.18 (d, J=6.2 Hz, 1H), 6.09 (br. s., 1H), 3.86-3.62 (m, 1H), 2.74-2.60 (m, 1H), 1.41 (s, 6H).

The Examples in Table 2 below were prepared according to the general procedure described in Example 1 by substitution of 2-(trifluoromethyl)benzaldehyde with the appropriate commercially available aldehyde as described in the preparation of Intermediate 1A, and Example 14 by substitution of (4-(2-hydroxypropan-2-yl)phenyl) boronic acid with the appropriate commercially available boronic acid or boronic ester as described in last step in the preparation of Example 14. Diastereomeric mixtures are designated as 'DM'. In cases where enantiomers were isolated the analytical data for each is included and designated as 'e1', 'e2', 'e3', and 'e4'.

TABLE 2

| Ex. No. | Structure | MS (M + 1)   | HPLC Ret. Time (min)                         | HPLC Method                      |
|---------|-----------|--|--|----------------------------------|
| 15      |           | 453.88(DM)<br>454.1(e1)<br>454.3(e2)<br>454.28(e4)   | 1.77(DM)<br>1.85(e1)<br>1.85(e2)<br>1.87(e4) | B(DM)<br>A(e1)<br>B(e2)<br>B(e4) |
| 16      |           | 456.21(DM)<br>455.86(e2)<br>455.79(e3)<br>455.84(e4) | 1.72(DM)<br>1.57(e2)<br>1.57(e3)<br>1.58(e4) | B(DM)<br>B(e2)<br>B(e3)<br>B(e4) |
| 17      |           | 483.08(DM)   | 1.80(DM)                                     | B(DM)                            |

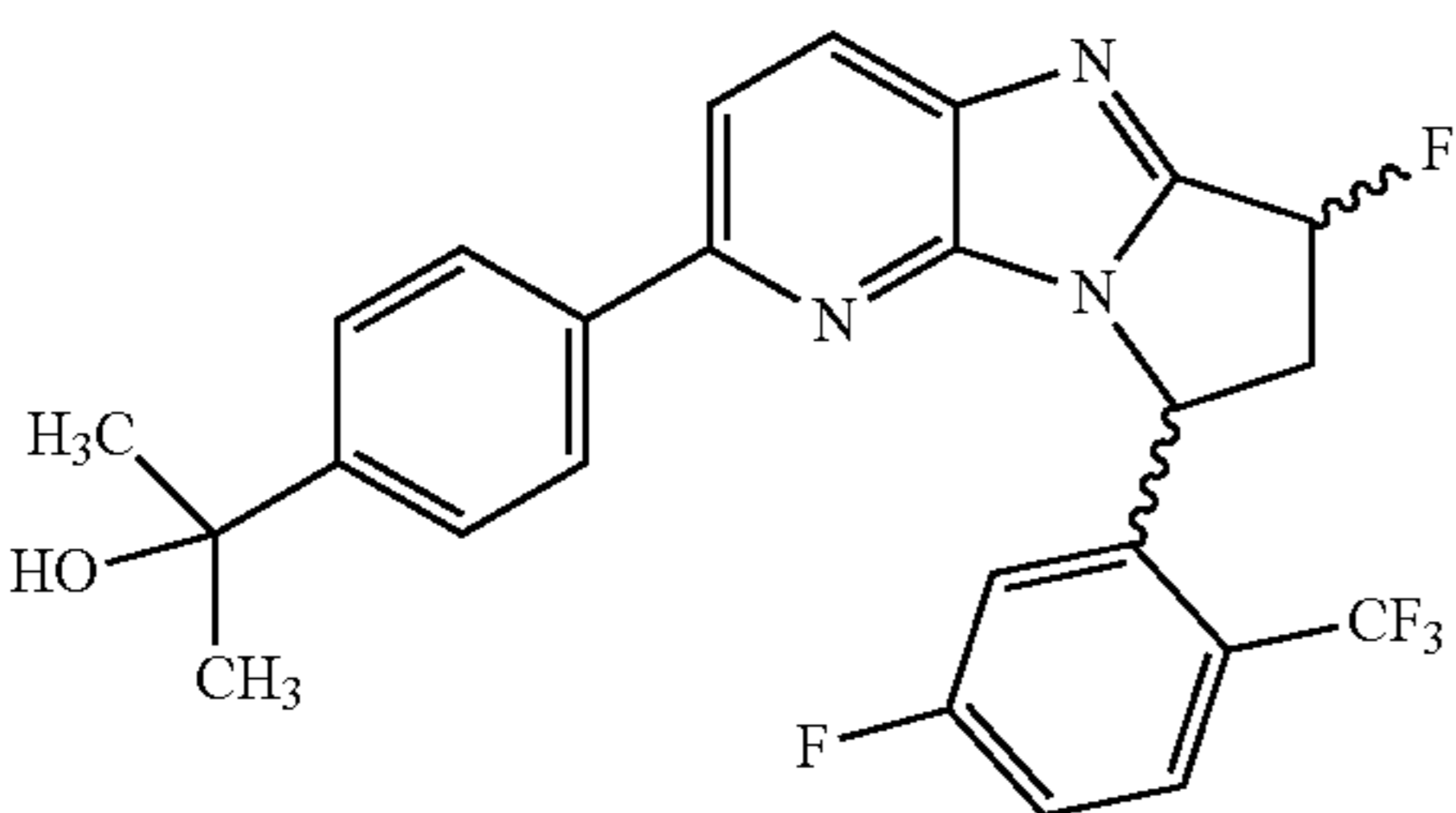


TABLE 2-continued

| Ex. No. | Structure | MS (M + 1)   | HPLC Ret. Time (min)                         | HPLC Method                      |
|---------|-----------|--|--|----------------------------------|
| 18      |           | 426.92(DM)<br>426.85(e1)<br>426.84(e2)               | 1.87(DM)<br>1.76(e1)<br>1.75(e2)             | B(DM)<br>A(e1)<br>A(e2)          |
| 19      |           | 399.92(e3)   | 1.63(e3)                                     | B(e3)                            |
| 20      |           | 417.96(DM)   | 1.78(DM)                                     | A(DM)                            |
| 21      |           | 428.09(e1)<br>428.34(e2)<br>427.96(e3)<br>428.23(e4) | 2.02(e1)<br>2.02(e2)<br>2.04(e3)<br>2.04(e4) | B(e1)<br>B(e2)<br>B(e3)<br>B(e4) |
| 22      |           | 472.24(e1)<br>472.17(e2)<br>472.32(e3)<br>472.04(e4) | 1.97(e1)<br>2.04(e2)<br>2.01(e3)<br>2.01(e4) | B(e1)<br>B(e2)<br>B(e3)<br>B(e4) |
| 23      |           | 474.17(e1)<br>474.18(e2)<br>474.32(e3)<br>474.16(e4) | 2.00(e1)<br>2.01(e2)<br>1.91(e3)<br>1.95(e4) | A(e1)<br>B(e2)<br>B(e3)<br>B(e4) |

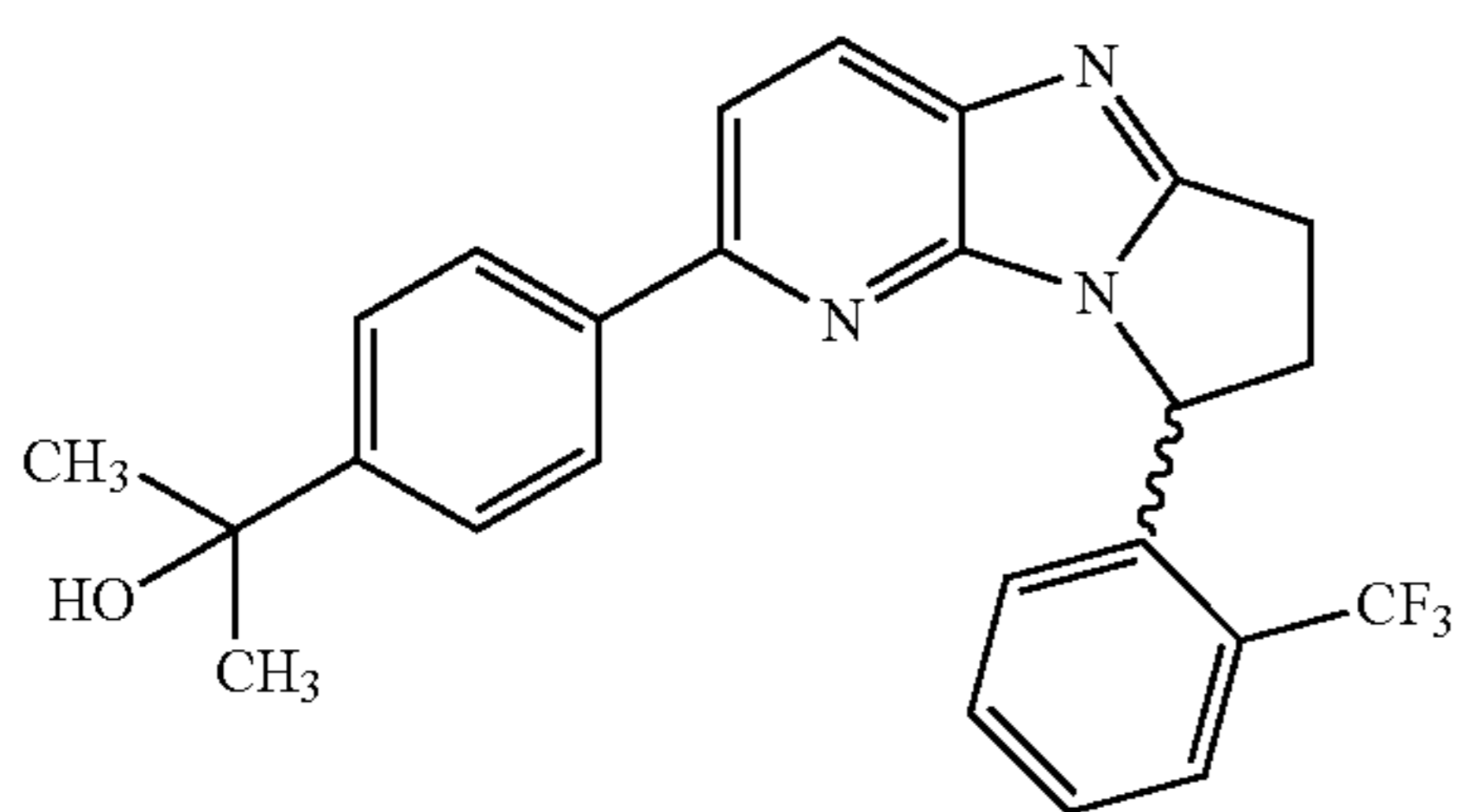


TABLE 2-continued

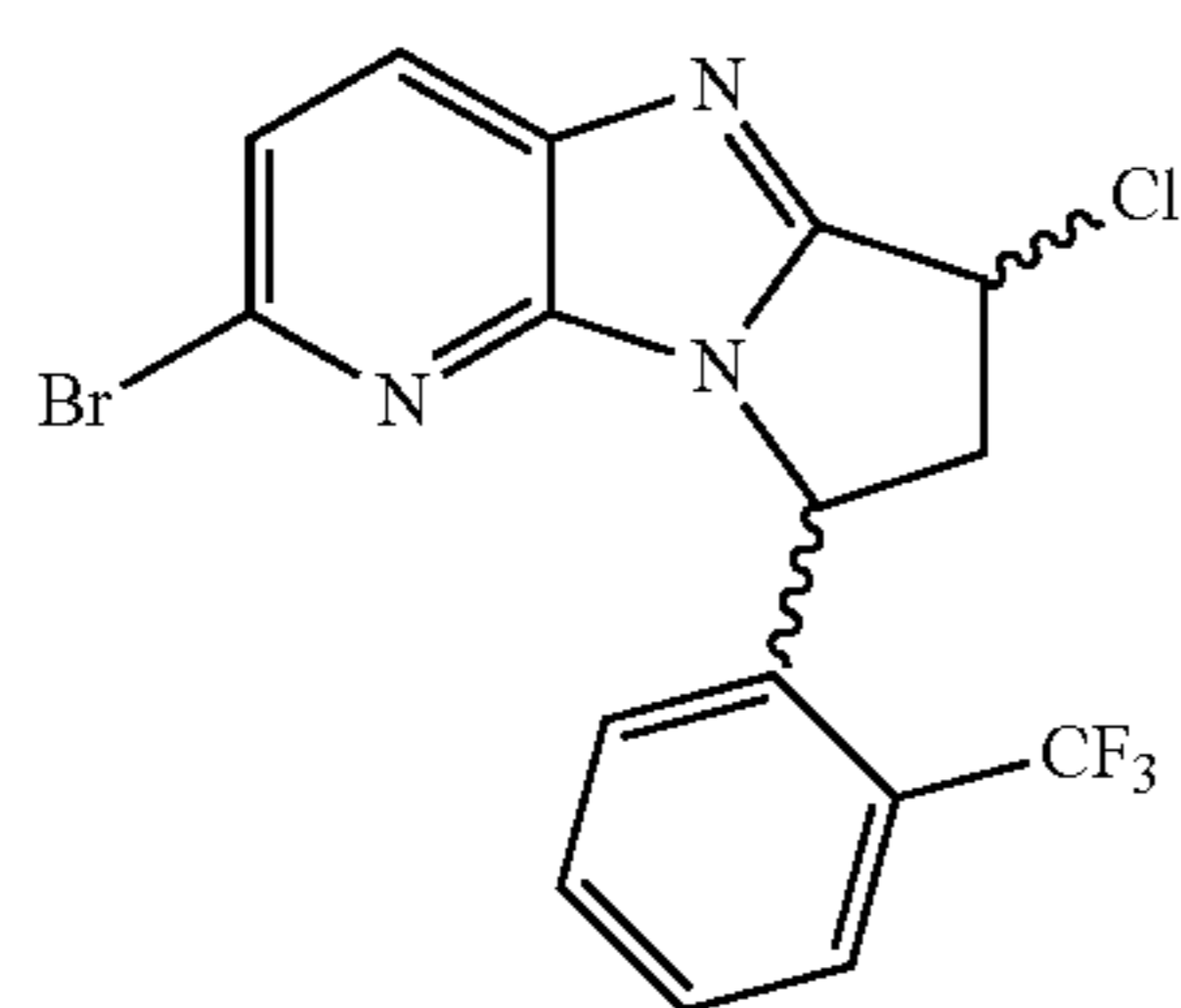
| Ex. No. | Structure   | MS (M + 1)   | HPLC Ret. Time (min)                                     | HPLC Method                               |
|---------|---|--|--|---|
| 24      |  | 474.18(DM)<br>474.18(e1)<br>473.94(e2)<br>474.25(e3)<br>473.92(e4) | 2.04(DM)<br>2.04(e1)<br>2.03(e2)<br>1.91(e3)<br>2.01(e4) | B(DM)<br>B(e1)<br>A(e2)<br>A(e3)<br>A(e4) |

## Example 25

2-(4-(8-(2-(Trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol



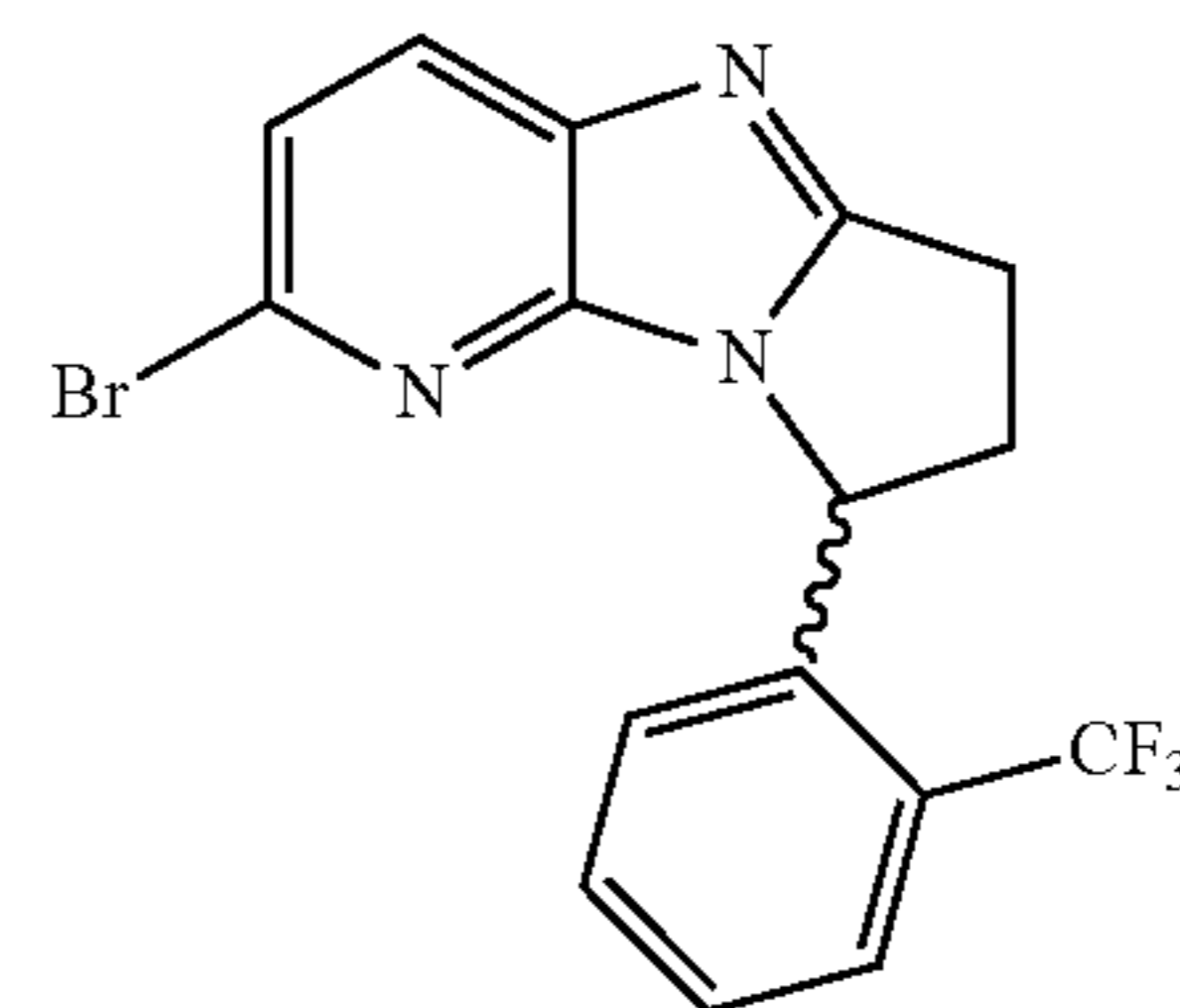
Intermediate 25A: 2-Bromo-6-chloro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine



N,N-Diisopropylethylamine (0.1 mL, 0.603 mmol) was added to a suspension of 2-bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (0.12 g, 0.301 mmol) in POCl<sub>3</sub> (1.7 mL, 18.08 mmol) at room temperature. The vial was flushed with N<sub>2</sub> and sealed. The stirred solution was heated at 60° C. for 75 minutes. After 1 h the reaction mixture was analyzed by LCMS and the reaction was judged to be complete (m/z 435.9, 2 diastereomeric peaks, M+H for desired product). The reaction mixture was concentrated to dryness under reduced pressure to yield a tan-brown oil. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and purified by silica gel chromatography (Teledyne-Isco REDISEP® Rf 12 g column),

eluting with 0-5% methanol in CH<sub>2</sub>Cl<sub>2</sub>, 12 minute gradient. Yield: 90.7 mg of a tan-brown solid (72.2%). LCMS: 2 diastereomeric peaks, each m/z 433.9/435.9 (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.10 (d, J=8.4 Hz, 0.50H), 8.08 (d, J=8.4 Hz, 0.50H), 7.82-7.76 (m, 1H), 7.76-7.67 (m, 1H), 7.55 (dt, J=12.1, 7.5 Hz, 1H), 7.47 (t\*, J=8.4 Hz, 1H), 6.14 (t, J=7.3 Hz, 1H), 6.05-5.94 (m, 2H), 5.79 (dd, J=8.7, 6.0 Hz, 2H), 3.79-3.66 (m, 2H). \*un-resolved diastereomeric doublets.

Intermediate 25-B: 2-Bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine



A solution of Intermediate 25A, (2-bromo-6-chloro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine) (90 mg, 0.217 mmol) was added to a suspension Raney Nickel in ethanol (2.2 mL). The mixture was stirred at room temperature under a H<sub>2</sub>-filled balloon for 20 hr at which point LCMS indicated a complete reaction (m/z 383.9 w/Br-pattern, M+H for desired product). The reaction mixture was filtered through a 25 mm syringe filter with a 0.45 Nylon membrane, and the filtrate was concentrated under vacuum to yield 90.2 mg of a pale tan solid (109%). LCMS: m/z 382.0 w/Br-pattern (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.87 (d, J=7.0 Hz, 1H), 7.67-7.51 (m, 3H), 7.41 (br. s., 1H), 6.89 (br. s., 1H), 5.99 (br. s., 1H), 3.27-3.06 (m, 2H), 2.45-2.29 (m, 2H). The crude product was used without further purification in the next step.

## Example 25

A solution of Intermediate 25B (2-bromo-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine) (35.0 mg, 92 μmol) and (4-(2-hydroxypropan-2-yl)phenyl)boronic acid (19.8 mg, 110 μmol) in dioxane (1 mL) and tripotassium phosphate (2.0 M aq solution) (140 μl, 275 μmol) was degassed for several



minutes with N<sub>2</sub>. While still degassing, 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (1.8 mg, 2.80 μmol) mmol) was added. The vial was sealed and heated at 90° C. with stirring for 70 minutes. The reaction mixture was analyzed by LCMS analysis at this point and judged to be incomplete. Additional boronic acid (9.0 mg, 0.54 eq) was added at room temperature, the reaction mixture was degassed, and additional 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (1.8 mg, 2.80 μmol) was added, the vial was sealed, and heating at 90° C. with stirring was carried out for 30 minutes, at which point at which point the reaction was analyzed by LCMS and judged to be complete (m/z 438.3, M+H for desired product). The reaction mixture was diluted with methanol and filtered through a 13 mm syringe filter with a 0.45 μ Nylon membrane, and the filtrate was purified by prep HPLC under the following conditions: The crude material was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19×200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Gradient: 20-60% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

The material was further purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19×200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-70% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

The yield of the product was 17.8 mg (44% yield). Two analytical LC/MS injections were used to determine the final purity. Injection 1 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm. Injection 2 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm. Proton NMR was acquired in deuterated DMSO.

Approximately 14.6 mg sample was resolved by chiral chromatography. The fractions ("Peak-1" and "Peak-2")

were collected in MeOH. The stereoisomeric purity of each fraction was estimated to be greater than 99.0% based on the prep-SFC chromatograms.

Preparative chromatographic conditions: Instrument: Berger Prep SFC MGII (LVL-L4621 Lab). Column: Lux Cellulose 4 25×3 cm ID, 5 μm. Flow rate: 85.0 mL/min. Mobile Phase: 70/30 CO<sub>2</sub>/MeOH Detector Wavelength: 220 nm Sample Prep and Inj. Volume: 1500 μL of 14.6 mg dissolved in 2 mL MeOH/ACN. Analytical Chromatographic Conditions: Instrument: Aurora analytical SFC (LVL-L4021 Lab). Column: Lux Cellulose 4 250×4.6 mm ID, 5 μm. Flow rate: 2.0 mL/min Mobile Phase: 70/30 CO<sub>2</sub>/MeOH Separations were done on parallel SFC system. Retention may vary slightly due to small flow rate variation.

Yield of individual enantiomers (absolute stereochemistry undetermined):

7.5 mg (9.93%), 99% pure, enantiomer 1. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.03 (d, J=8.3 Hz, 1H), 7.86 (d, J=7.2 Hz, 1H), 7.74 (d, J=8.2 Hz, 3H), 7.59-7.50 (m, 2H), 7.45 (d, J=8.2 Hz, 2H), 6.99 (d, J=7.4 Hz, 1H), 6.00 (br. s., 1H), 5.07 (s, 1H), 3.32-3.21 (m, 2H), 3.20-3.07 (m, 1H), 2.48-2.41 (m, 1H), 1.40 (s, 6H).

8.3 mg (7.05%), 93% pure, enantiomer 2. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.03 (d, J=8.3 Hz, 1H), 7.86 (d, J=7.2 Hz, 1H), 7.74 (d, J=8.2 Hz, 3H), 7.59-7.50 (m, 2H), 7.45 (d, J=8.2 Hz, 2H), 6.99 (d, J=7.4 Hz, 1H), 6.00 (br. s., 1H), 5.07 (s, 1H), 3.32-3.21 (m, 2H), 3.20-3.07 (m, 1H), 2.48-2.41 (m, 1H), 1.40 (s, 6H).

Two analytical LC/MS injections were used to determine the final purity.

Injection 1 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

Injection 2 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50° C.; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

The Examples in Table 3 below were prepared according to the general procedure described in Example 1 by substitution of 2-(trifluoromethyl)benzaldehyde with the appropriate aldehyde as described in the preparation of Intermediate 1A, and Example 25 by substitution of (4-(2-hydroxypropan-2-yl)phenyl)boronic acid with the appropriate commercially available boronic acid or boronic ester as described in Step 25-C. Racemic mixtures are designated as 'rac'. In cases where enantiomers were isolated the analytical data for each is included and designated as 'e1' and 'e2'.

TABLE 3

| Ex. No. | Structure | MS (M + 1)  | HPLC Ret. Time (min) | HPLC Method |
|---------|-----------|-------------|----------------------|-------------|
| 26      |           | 436.26(rac) | 1.72(rac)            | B(rac)      |
|         |           | 436.26(e1)  | 1.70(e1)             | B(e1)       |
|         |           | 436.25(e2)  | 1.70(e2)             | B(e2)       |

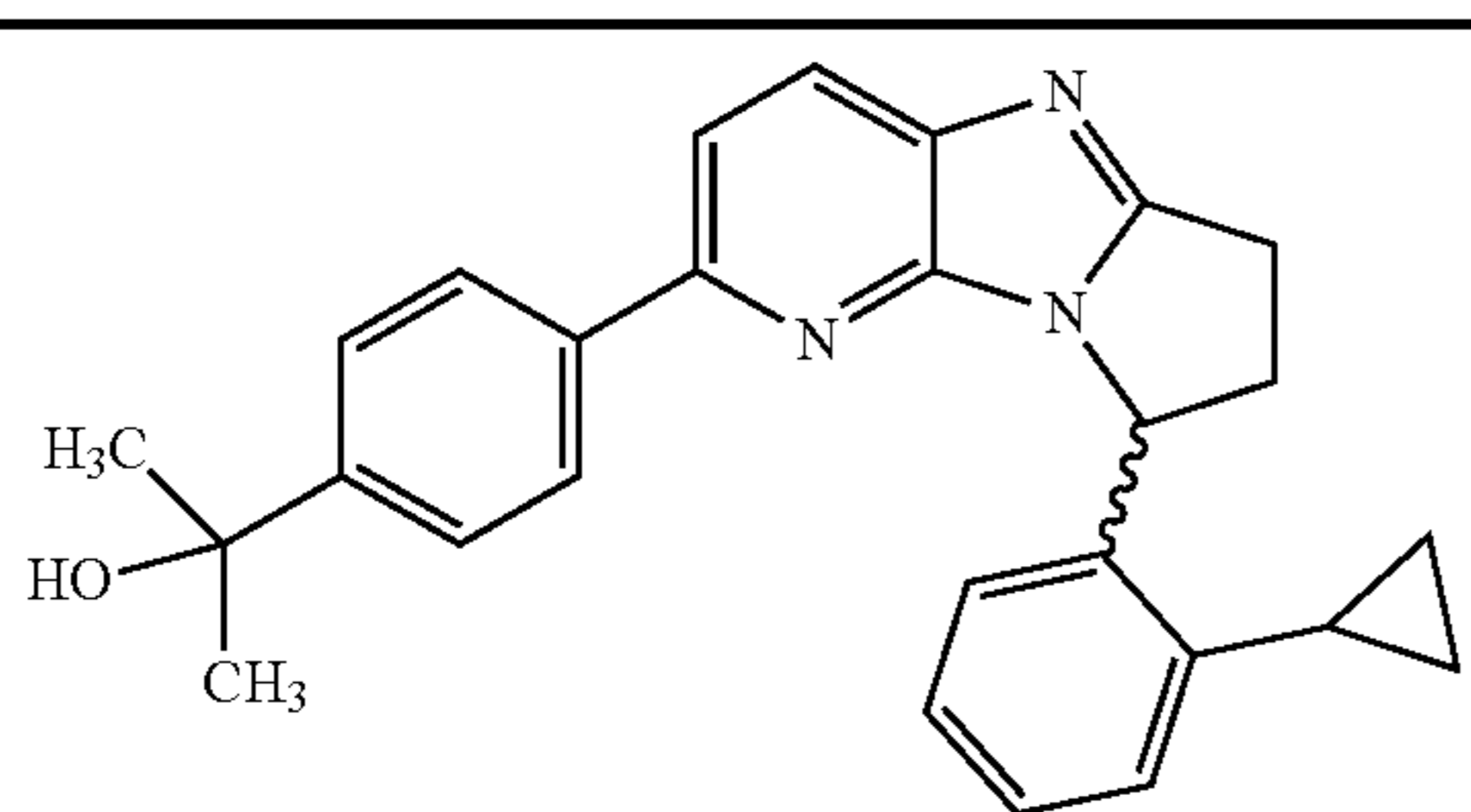
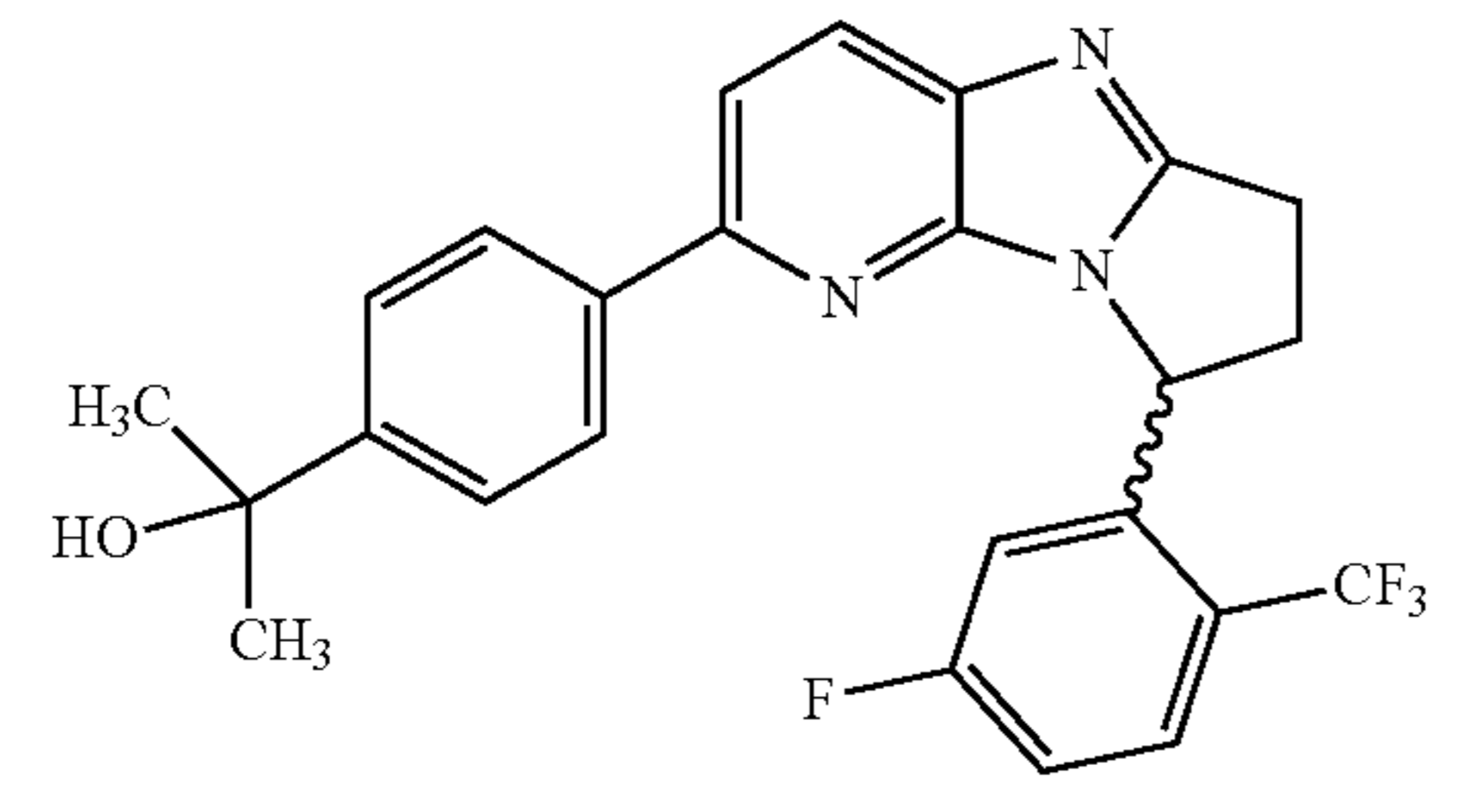
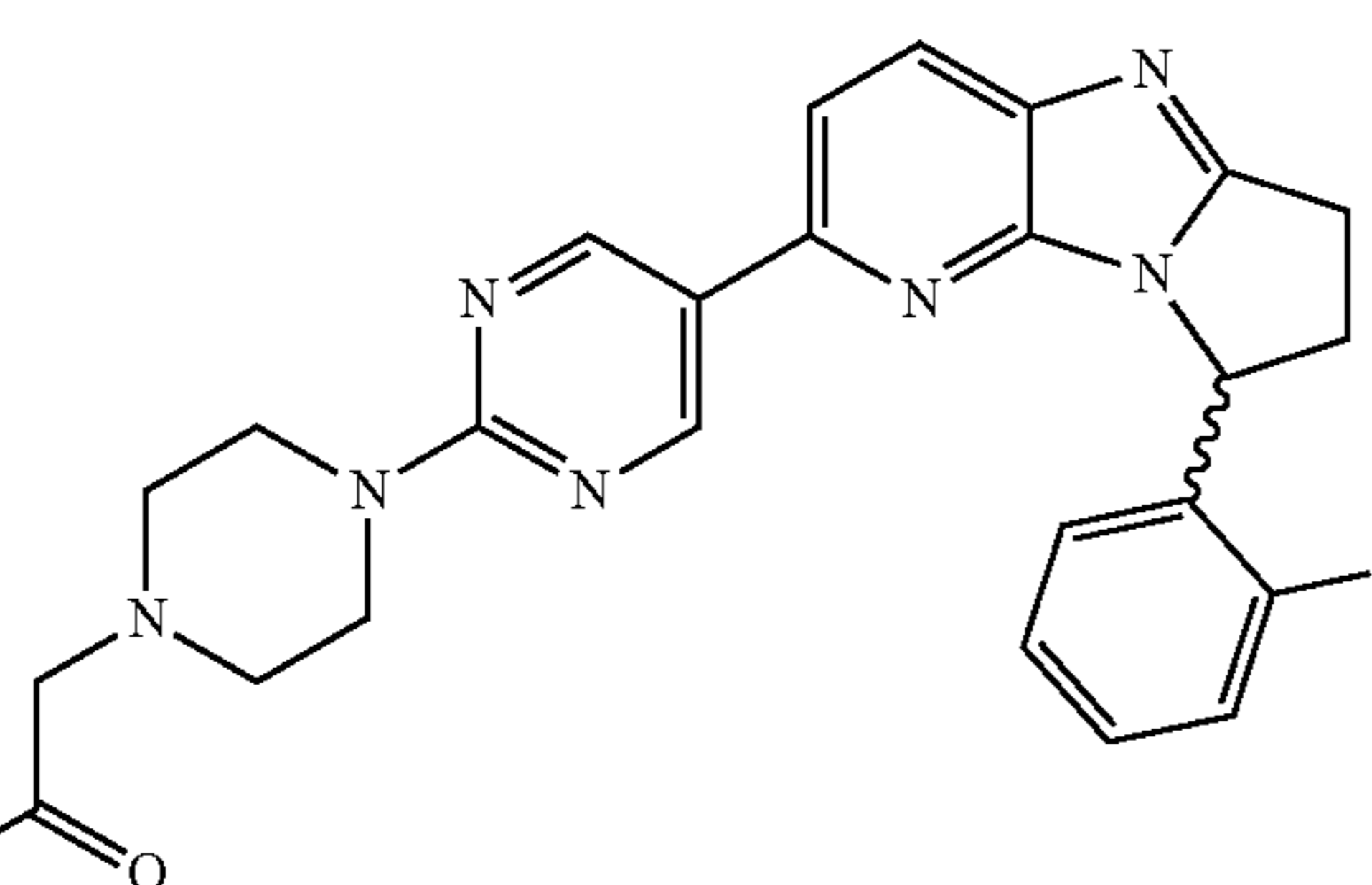


TABLE 3-continued

| Ex. No. | Structure | MS (M + 1)                              | HPLC Ret. Time (min)              | HPLC Method              |
|---------|-----------|---|-----------------------------------|--------------------------|
| 27      |           | 437.87(rac)<br>437.90(e2)               | 1.56(rac)<br>1.22(e2)             | B(rac)<br>A(e2)          |
| 28      |           | 465.28(rac)                             | 1.74(rac)                         | B(rac)                   |
| 29      |           | 409.24(rac)<br>408.86(e2)               | 1.83(rac)<br>1.84(e2)             | B(rac)<br>B(e2)          |
| 30      |           | 382.16(rac)<br>382.20(e2)               | 1.42(rac)<br>1.53(e2)             | B(rac)<br>B(e2)          |
| 31      |           | 400.32(e1)                              | 1.34(e1)                          | A(e1)                    |
| 32      |           | 455.86(rac)<br>456.22(e1)<br>456.25(e2) | 1.81(rac)<br>1.90(e1)<br>1.90(e2) | B(rac)<br>B(e1)<br>B(e2) |

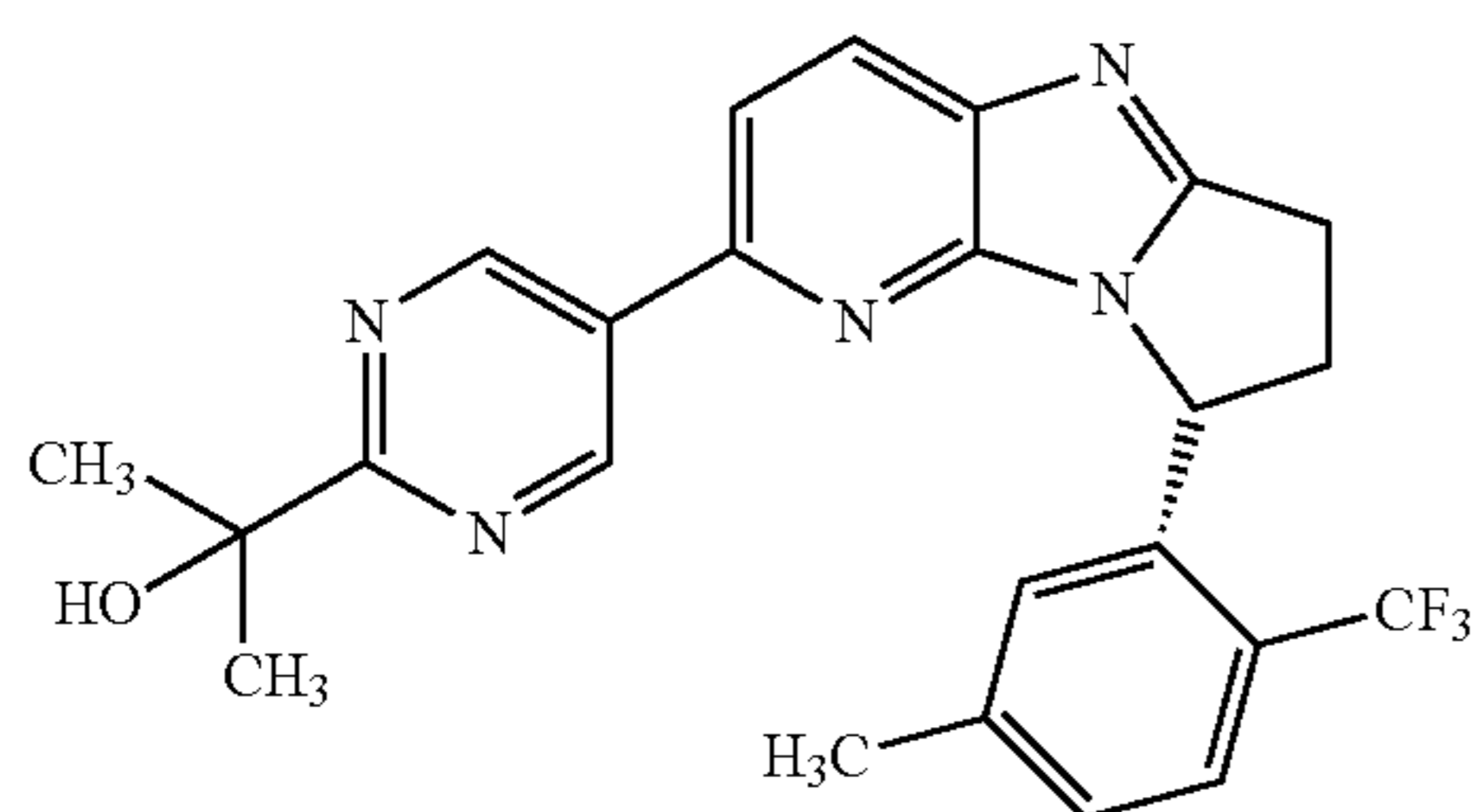


TABLE 3-continued

| Ex. No. | Structure  | MS (M + 1)                              | HPLC Ret. Time (min)              | HPLC Method              |
|---------|--|---|-----------------------------------|--------------------------|
| 33      |    | 410.16(e1)<br>410.16(e2)                | 1.95(e1)<br>1.96(e2)              | B(e1)<br>B(e2)           |
| 34      |   | 456.24(rac)<br>456.20(e1)<br>456.28(e2) | 1.88(rac)<br>2.00(e1)<br>1.58(e2) | B(rac)<br>B(e1)<br>A(e2) |
| 35      |  | 486.24(rac)                             | 1.28(rac)                         | A(rac)                   |

## Example 36

(R)-2-(5-(8-(2,5-Dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2,1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol



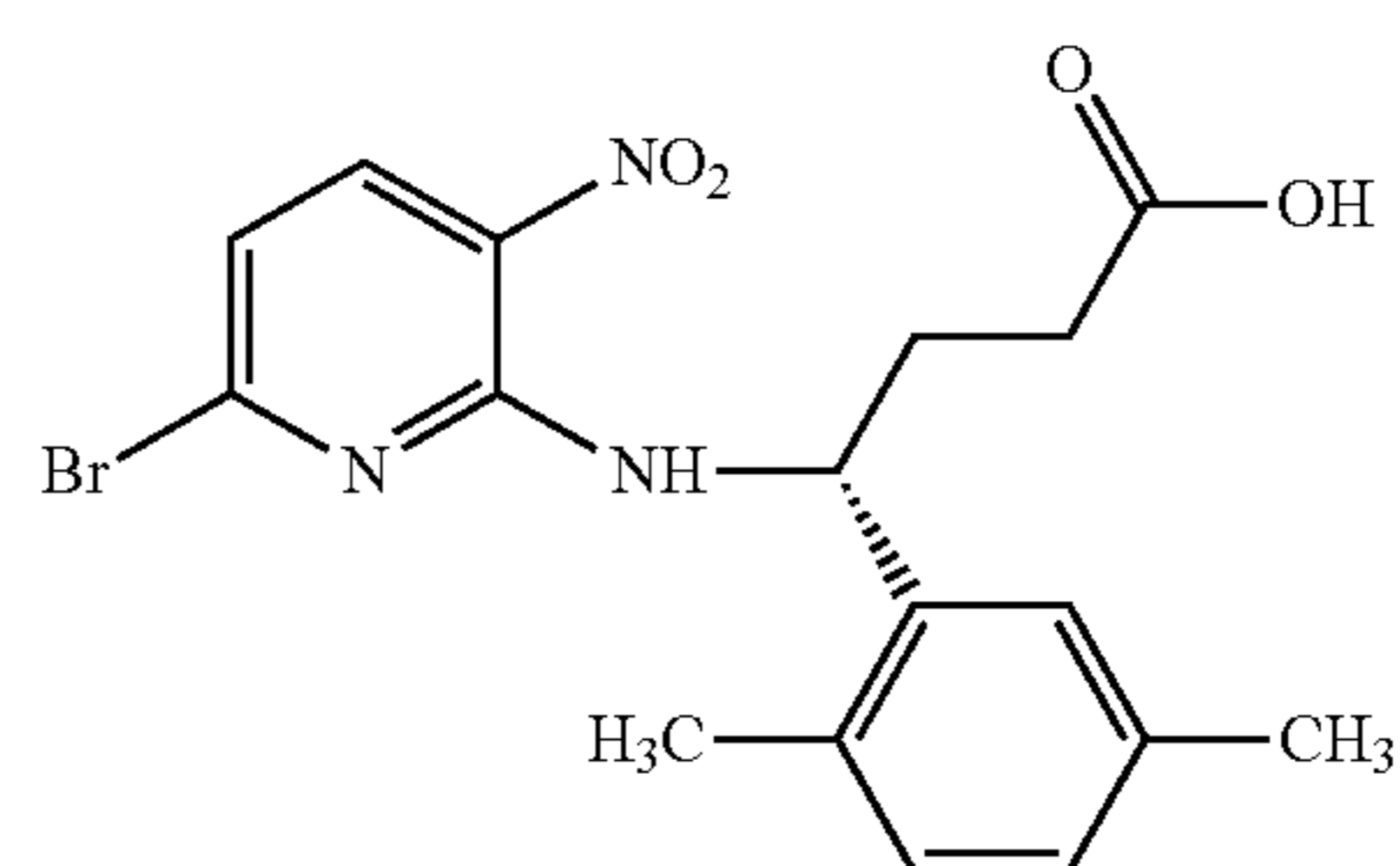
## Intermediate 36A: (R)-4-((6-Bromo-3-nitropyridin-2-yl)amino)-4-(2,5-dimethylphenyl)butanoic acid

50

(36)

55

60



(36A)

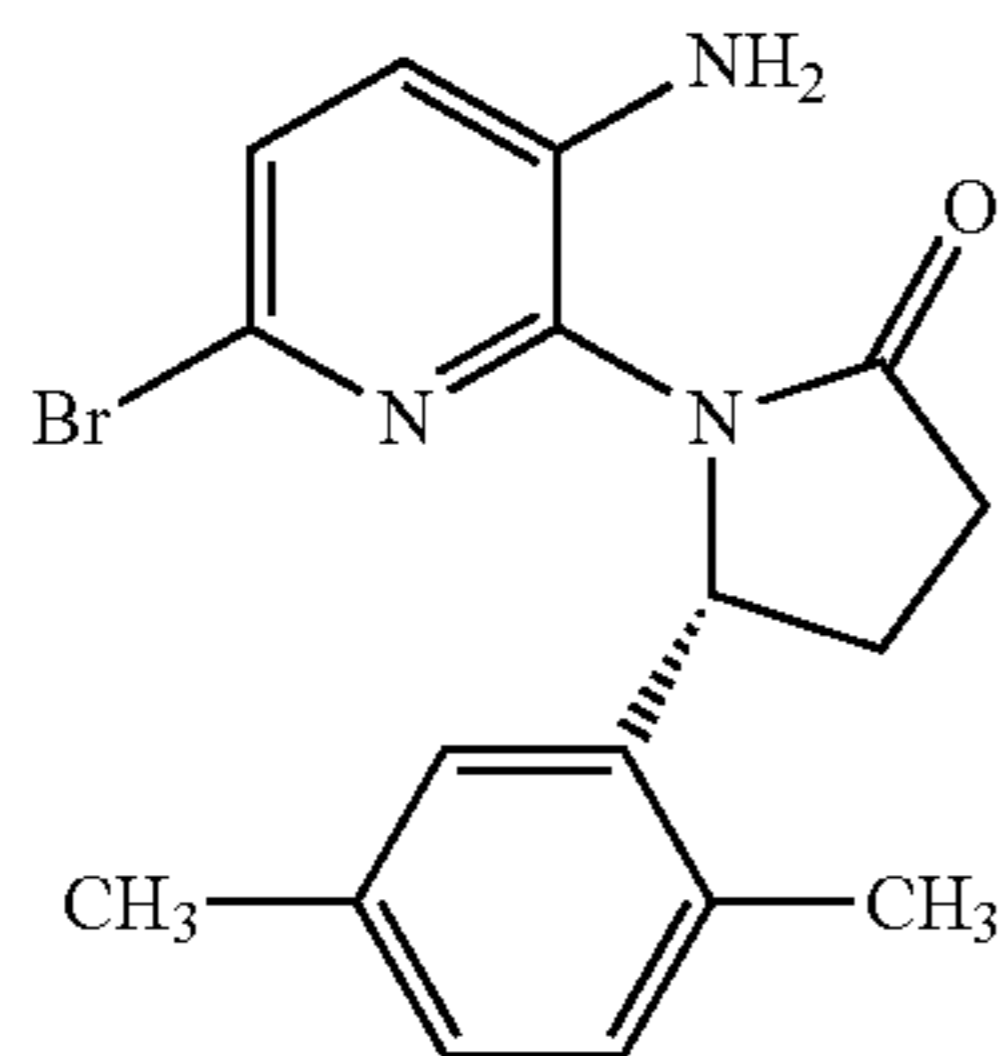
Sodium carbonate (0.68 g, 6.39 mmol) was added to a vigorously stirred solution of 2,6-dibromo-3-nitropyridine (0.50 g, 1.774 mmol) and (R)-4-amino-4-(2,5-dimethylphenyl)butanoic acid HCl (0.48 g, 1.95 mmol) in ethanol (18



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mL) under N<sub>2</sub> at room temperature for 7.5 h. After a several minutes, there was precipitation, which became more extensive with time. LCMS at that time indicated that the reaction was proceeding slowly. The reaction mixture was then stirred overnight at 40° C. The next morning, the oil bath temperature was then raised to 50° C., and stirring was continued for 9 h. At that time analysis of the reaction mixture by LCMS suggested the reaction was incomplete. Additional acid was added (22 mg, 0.05 eq), and stirring at 50° C. was continued for 16 h, heating was continued at 60° C. for 3 h at which time the reaction mixture was analyzed by LCMS and judged to be complete (m/z 407.9 w/Br-pattern, M+H for desired product). After cooling to room temperature, the volatiles were removed under reduced pressure. The reaction mixture was acidified with 1N HCl (ca. 15 mL), which caused some precipitation. EtOAc was added, the layers were separated, the EtOAc layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 0.78 g of an oily yellow solid. Flash chromatography on silica gel (Teledyne-Isco REDISEP® Rf 40 g column), eluting with 0-100% EtOAc in hexanes, 15 min. gradient, yielded 0.61 g of a yellow solid (84%). LCMS: m/z 409.8 w/Br-pattern (M+H). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 12.19 (br. s., 1H), 8.77 (d, J=7.6 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.27 (s, 1H), 7.04 (d, J=7.7 Hz, 1H), 6.94 (d, J=1.1 Hz, 1H), 6.91 (d, J=8.4 Hz, 1H), 5.46-5.30 (m, 1H), 2.46 (s, 3H), 2.36-2.28 (m, 2H), 2.23 (s, 3H), 2.27-2.16 (m, 1H), 2.07-1.86 (m, 1H).

Intermediate 36B: (R)-1-(3-Amino-6-bromopyridin-2-yl)-5-(2,5-dimethylphenyl)pyrrolidin-2-one

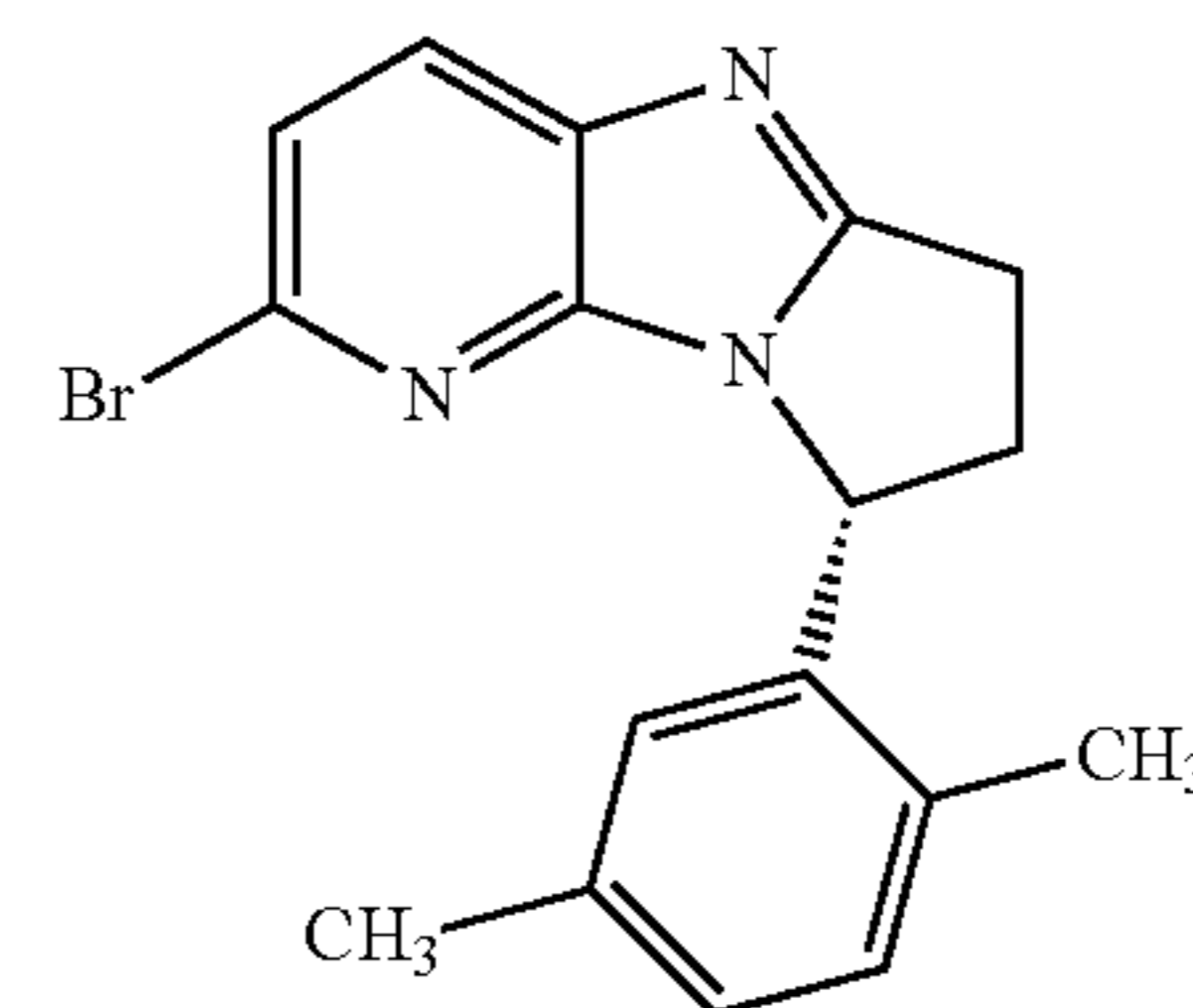


A solution of (R)-4-((3-amino-6-bromopyridin-2-yl)amino)-4-(2,5-dimethylphenyl)butanoic acid (51 mg, 0.134 mmol), BOP (120 mg, 0.268 mmol), and N,N-diisopropylethylamine (904 μL, 0.535 mmol) in DMF (1339 μL) was stirred at room temperature under N<sub>2</sub> for 50 min. At that time the reaction was judged complete after analysis of the reaction mixture by LCMS (m/z 362.0 w/Br-pattern, M+H for desired product). The volatiles were removed under reduced pressure and EtOAc and 10% aq LiCl solution were added, the layers were separated, the EtOAc layer was washed with 10% aq LiCl solution, saturated aqueous NaHCO<sub>3</sub> solution, brine, and the organic layer dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 0.82 g of a tan-brown solid. Flash chromatography on silica gel (Teledyne-Isco REDISEP® 4 g column), eluting with 0-100% EtOAc in hexanes, 12 minute gradient, yielded 31.6 mg of a tan oil. The oil was stored over hexanes for the weekend. The hexanes were decanted off, and residual hexane was removed from the chromatographed product under vacuum. Yield: 32.0 mg of a tan-brown oil (65.5%). LCMS: m/z

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362.0 w/Br-pattern (M+H). The product was used for the next without further purification.

Intermediate 36C: (R)-2-Bromo-8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine



(36C)

A solution of (R)-1-(3-amino-6-bromopyridin-2-yl)-5-(2,5-dimethylphenyl)pyrrolidin-2-one (31.8 mg, 0.088 mmol) in acetic acid (1.2 mL) with 8.21 microliters of concentrated H<sub>2</sub>SO<sub>4</sub> was heated at 80° C. for 20 minutes. The acetic acid solution of the substrate was initially green but turned tan as soon as the sulfuric acid was added. The reaction was analyzed by LCMS after 10 minutes and judged to be incomplete. The heating block temperature was increased to 120° C. and stirring was continued for 45 minutes. At this point the reaction mixture was analyzed by LCMS and the reaction judged to be complete (m/z 242.0 w/Br-pattern, M+H for desired product). The reaction mixture was concentrated to dryness under high vacuum. EtOAc and saturated aqueous NaHCO<sub>3</sub> solution were added, the layers were separated, the EtOAc layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield 14.3 mg of a tan oil (47.3%). LCMS: m/z 342.0 w/Br-pattern (M+H). The crude product was used as is for the next step.

## Example 36

A solution of (R)-2-bromo-8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (13.6 mg, 0.040 mmol) and 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)propan-2-ol (12.6 mg, 0.048 mmol) in dioxane (0.4 mL) and tripotassium phosphate (2.0 M aq solution) (54.0 μL, 0.108 mmol) was degassed for several minutes with N<sub>2</sub>. While still degassing, 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (2.6 mg, 3.97 μmol) mmol) was added. The vial was sealed and heated at 90° C. for 1 hr/15 min. At that time the reaction was analyzed by LCMS and judged to be incomplete. Additional boronic acid (6.3 mg, 0.60 eq) was added at room temperature and after degassing, additional 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (2.6 mg, 3.97 μmol) was also added. The vial was sealed, and heated at 90° C. for 45 min. At that time the reaction was analyzed by LCMS and as no change was observed from the first analysis the reaction was judged to be complete. The major component was desired product (m/z 400.1, M+H for desired product). The reaction mixture was cooled, diluted with methanol, and filtered through a 13 mm syringe filter with a 0.45 Nylon membrane, and the filtrate purified under the following conditions:

Column: XBridge C18, 19×200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammo-



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nium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 20-60% B over 19 minutes, then a 4-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

The yield of the product was 9.6 mg, and its estimated purity by LCMS analysis was 97%. Two analytical LC/MS injections were used to determine the final purity.

Injection 1 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7- $\mu$ m particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50° C.; Gradient: 0-100% B over

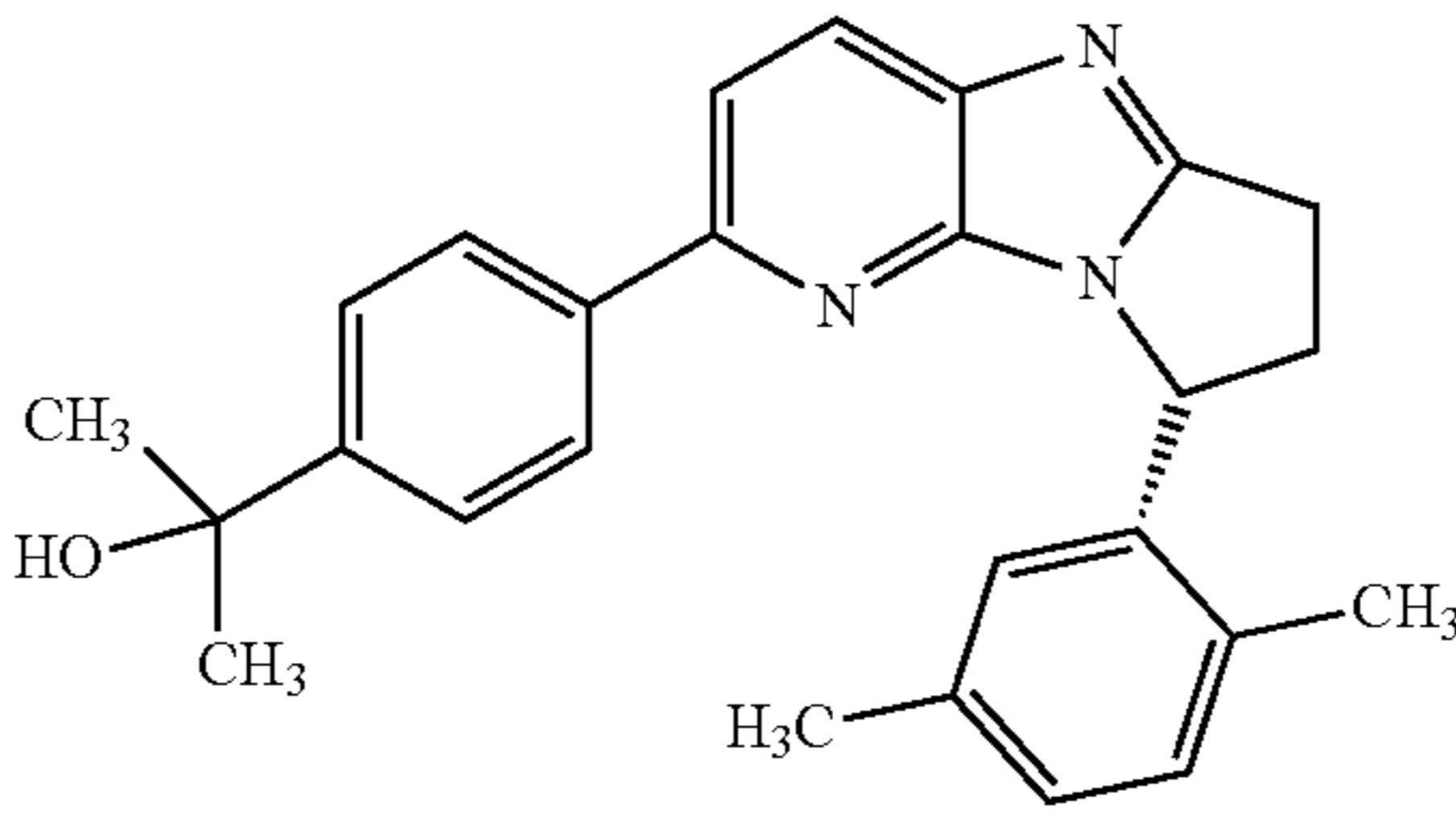
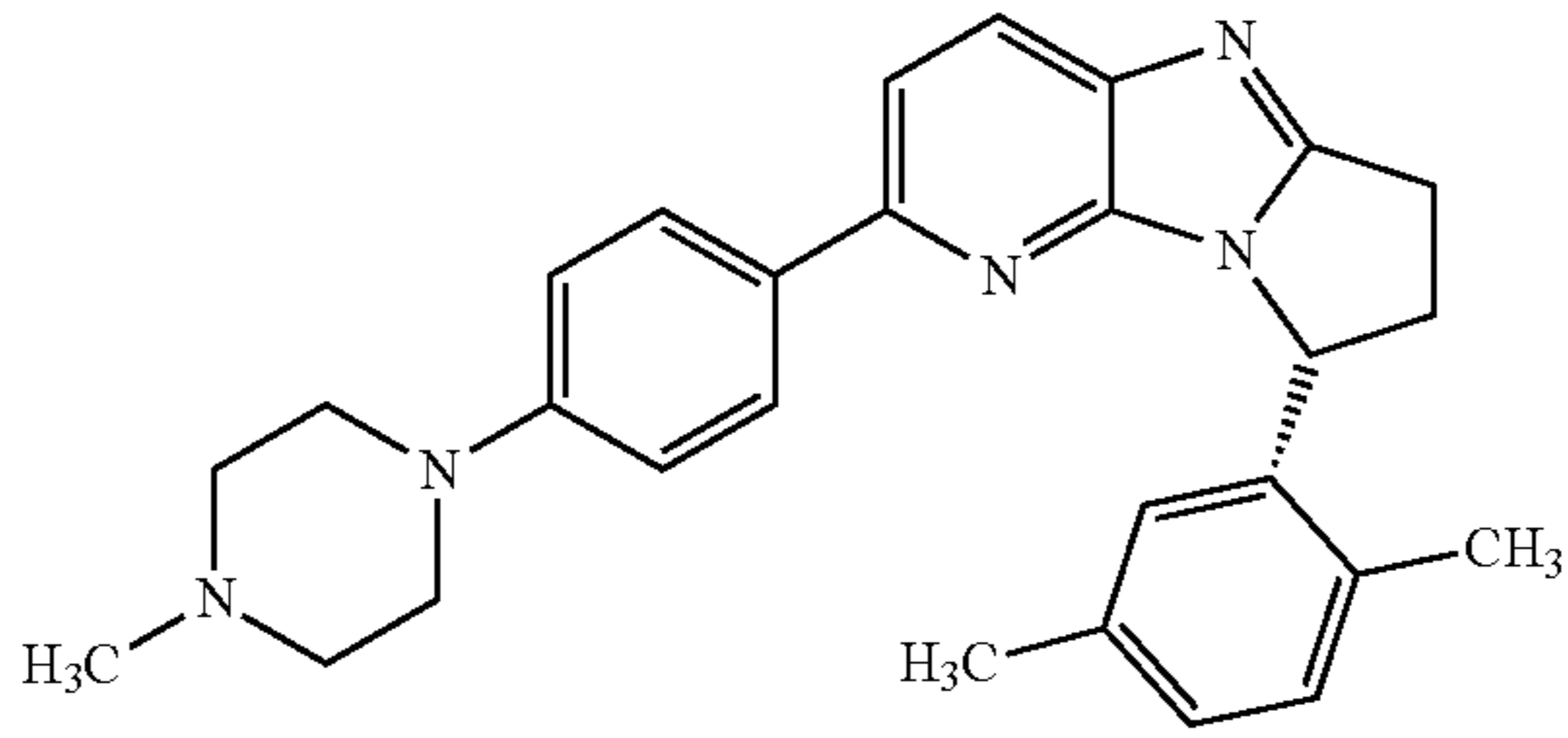
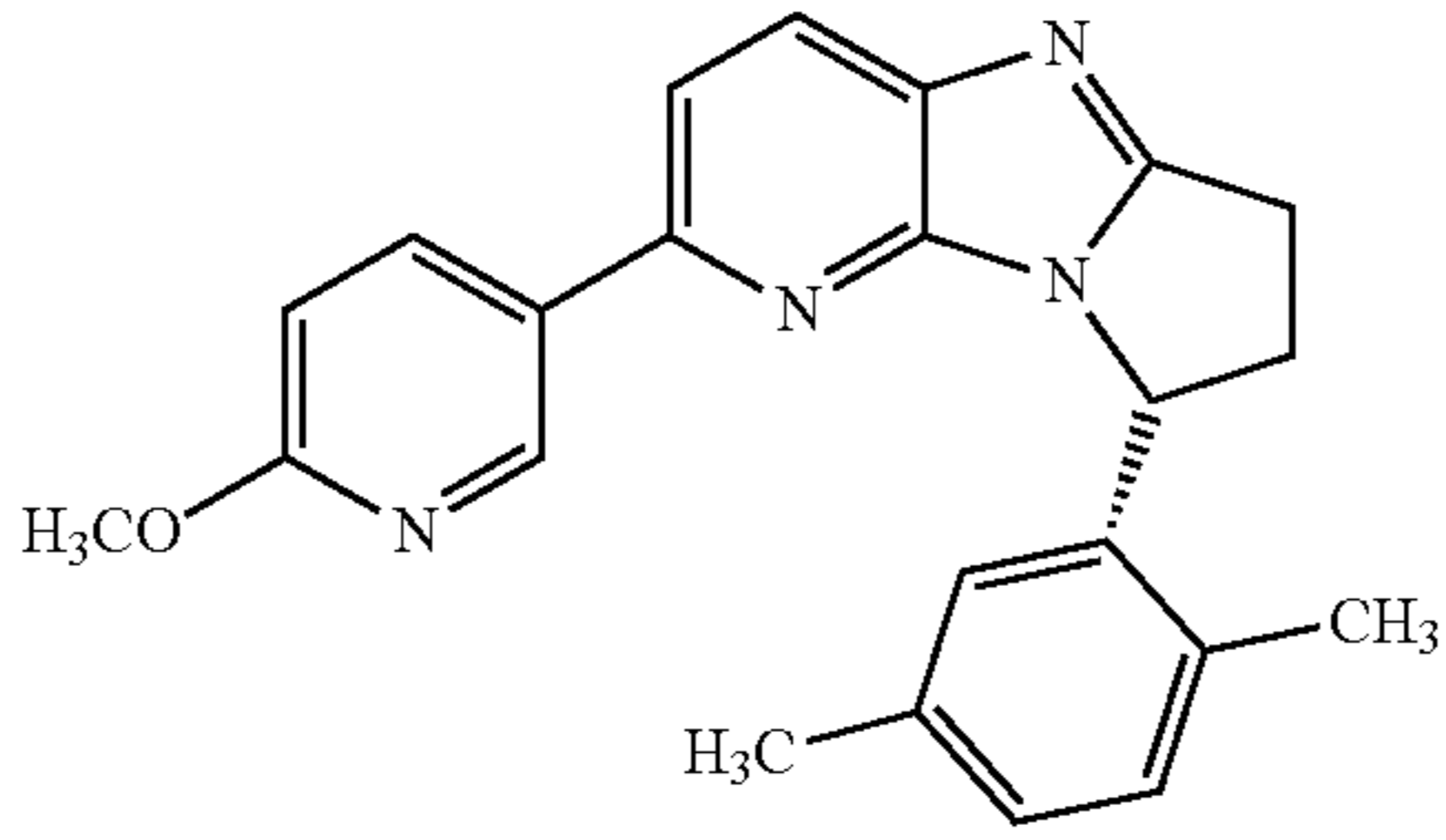
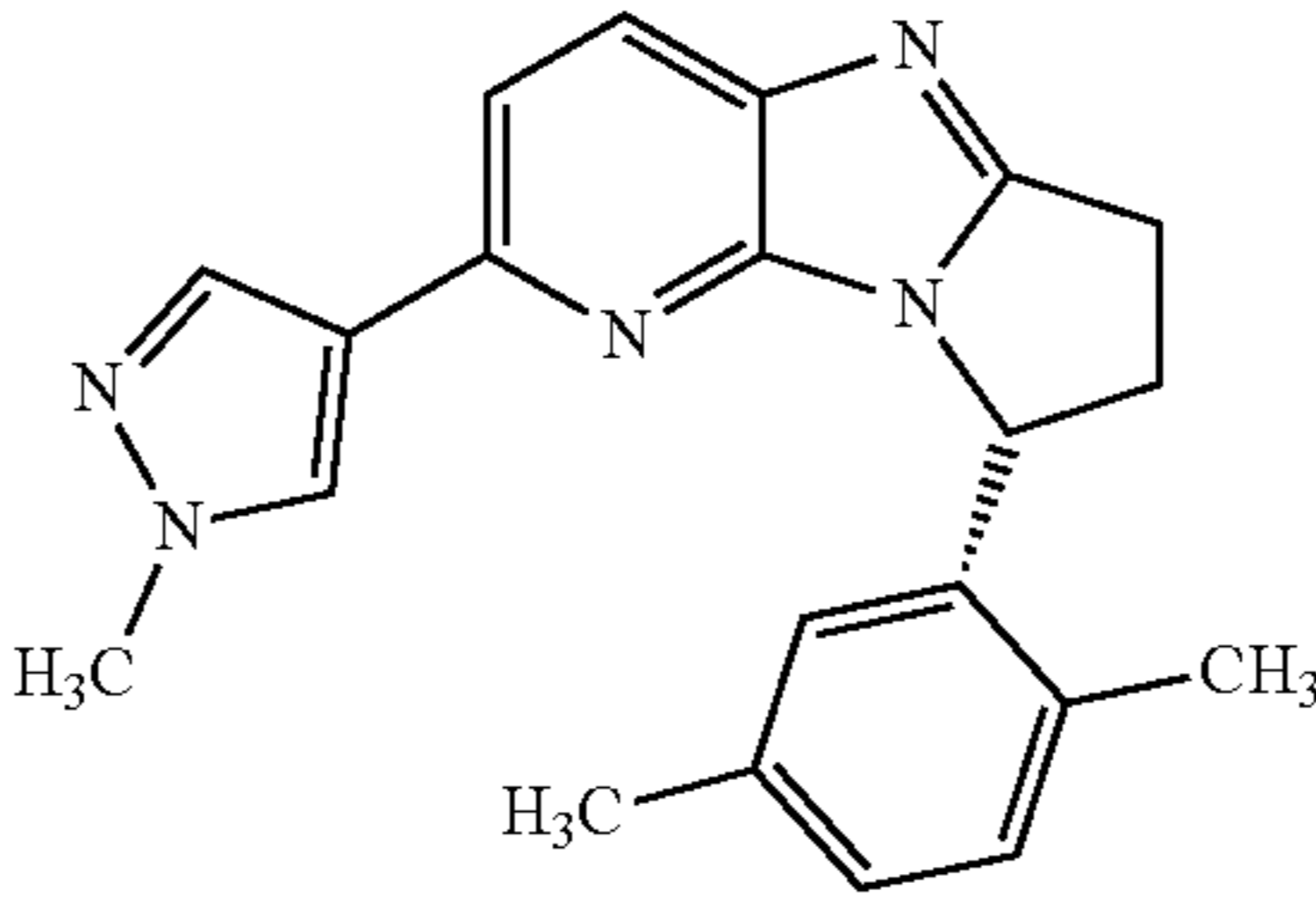
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3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

LCMS, purified product: m/z 400.1 (M+H), 799.2 (2M+H). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  9.21 (s, 2H), 8.16 (d, J=8.3 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.19 (s, 1H), 7.02 (d, J=7.8 Hz, 1H), 6.70 (s, 1H), 6.03-5.88 (m, 1H), 3.42-3.32 (m, 1H), 3.30-3.20 (m, 2H), 3.19-3.12 (m, 1H), 2.11 (s, 3H), 1.50 (s, 6H).

The Examples in Table 4 below were prepared according to the general procedure described in Example 36 by substitution of 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)propan-2-ol with the appropriate commercially available boronic acid or boronic ester as described in the last step in the preparation of Example 36.

TABLE 4

| Ex. No. | Structure  | MS (M + 1) | HPLC Ret. Time (min) | HPLC Method |
|---------|--|------------|----------------------|-------------|
| 37      |   | 398.1      | 1.82                 | B           |
| 38      |  | 438.1      | 1.63                 | B           |
| 39      |  | 371.2      | 1.57                 | B           |
| 40      |  | 344.0      | 1.50                 | B           |

3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

Injection 2 conditions: Column: Waters Acquity UPLC BEH C18, 2.1×50 mm, 1.7- $\mu$ m particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1% trifluoroacetic acid; Temperature: 50° C.; Gradient: 0-100% B over

## Biological Assays

The pharmacological properties of the compounds of this invention may be confirmed by a number of biological assays. The exemplified biological assays, which follow, have been carried out with compounds of the invention.



## TNF or CD40L-Induced HEK-Blue Assay

Test compounds serially diluted in DMSO were plated in an assay plate (Labcyte, Cat. #LP-0200) at final concentrations ranging from 0.004  $\mu\text{M}$  to 25  $\mu\text{M}$ . TNF $\alpha$  (final concentration 0.5 ng/ml) or CD40L (final concentration 30 ng/ml) in assay buffer [DMEM, 4.5 g/l glucose (Gibco, Cat. 21063-029), 10% FBS (Sigma, F4135), 1% Penicillin-Streptomycin (Gibco, Cat. 15140-122), 1% Anti-Anti (Gibco, Cat. 15240-112) and 2 mM L-glutamine (Gibco, Cat. 25030-081)] was then added to the assay plate. After a 30 minute pre-incubation at 37° C. and 5% CO<sub>2</sub>, HEK-Blue-CD40L cells (InvivoGen, Cat. Code hkb-cd40) containing a NF- $\kappa$ B-driven secreted alkaline phosphatase reporter gene were seeded into the assay plate at a density of 20,000 cells per well. This plate was then incubated for 18 h at 37° C. and 5% CO<sub>2</sub>. Secreted alkaline phosphatase expression was measured using QUANTI-Blue (InvivoGen, Cat. Code rep-qb1) according to manufacturer's specifications and the assay plate was read on a PerkinElmer Envision at 620 nm.

Inhibition data for the test compound over a range of concentrations was plotted as percentage inhibition of the test compound (100%=maximum inhibition). IC<sub>50</sub> values were determined after correcting for background [(sample read–mean of low control)/(mean of high control–mean of low control)] where by the low control is DMSO without stimulation and high control is DMSO with stimulation. The IC<sub>50</sub> is defined as the concentration of test compound which produces 50% inhibition and was quantified using the 4 parameter logistic equation to fit the data.

Table 5 lists the IC<sub>50</sub> values measured in the TNF induced HEK-Blue assay for Examples 1 to 40 of this invention. The results in Table 5 are reported as: "A" represents an IC<sub>50</sub> value of less than 1  $\mu\text{M}$ , "B" represents an IC<sub>50</sub> value in the range of 1  $\mu\text{M}$  to less than 10  $\mu\text{M}$ ; and "C" represents an IC<sub>50</sub> value in the range of 10  $\mu\text{M}$  to 25  $\mu\text{M}$ . The compounds of the present invention, as exemplified by Examples 1 to 40 showed IC<sub>50</sub> values measured in the TNF induced HEK-Blue assay of 25  $\mu\text{M}$  or less.

TABLE 5

| Ex. No. | TNF induced HEK-Blue assay IC <sub>50</sub> value |
|---------|---|
| 1       | A (e1)<br>B (e2)<br>B (e3)<br>B (e4)              |
| 2       | A (e1)<br>B (e2)<br>B (e3)<br>B (e4)              |
| 3       | A (e1)<br>A (e2)<br>A (e3)<br>B (e4)              |
| 4       | A (DM)  |
| 5       | A (DM)  |
| 6       | A (DM)  |
| 7       | B (DM)  |
| 8       | B (DM)  |
| 9       | A (e1)<br>A (e2)<br>B (e3)<br>B (e4)              |
| 10      | A (DM)  |
| 11      | A (e1)<br>B (e4)                                  |
| 12      | B (e2)<br>C (e3)<br>B (e4)                        |

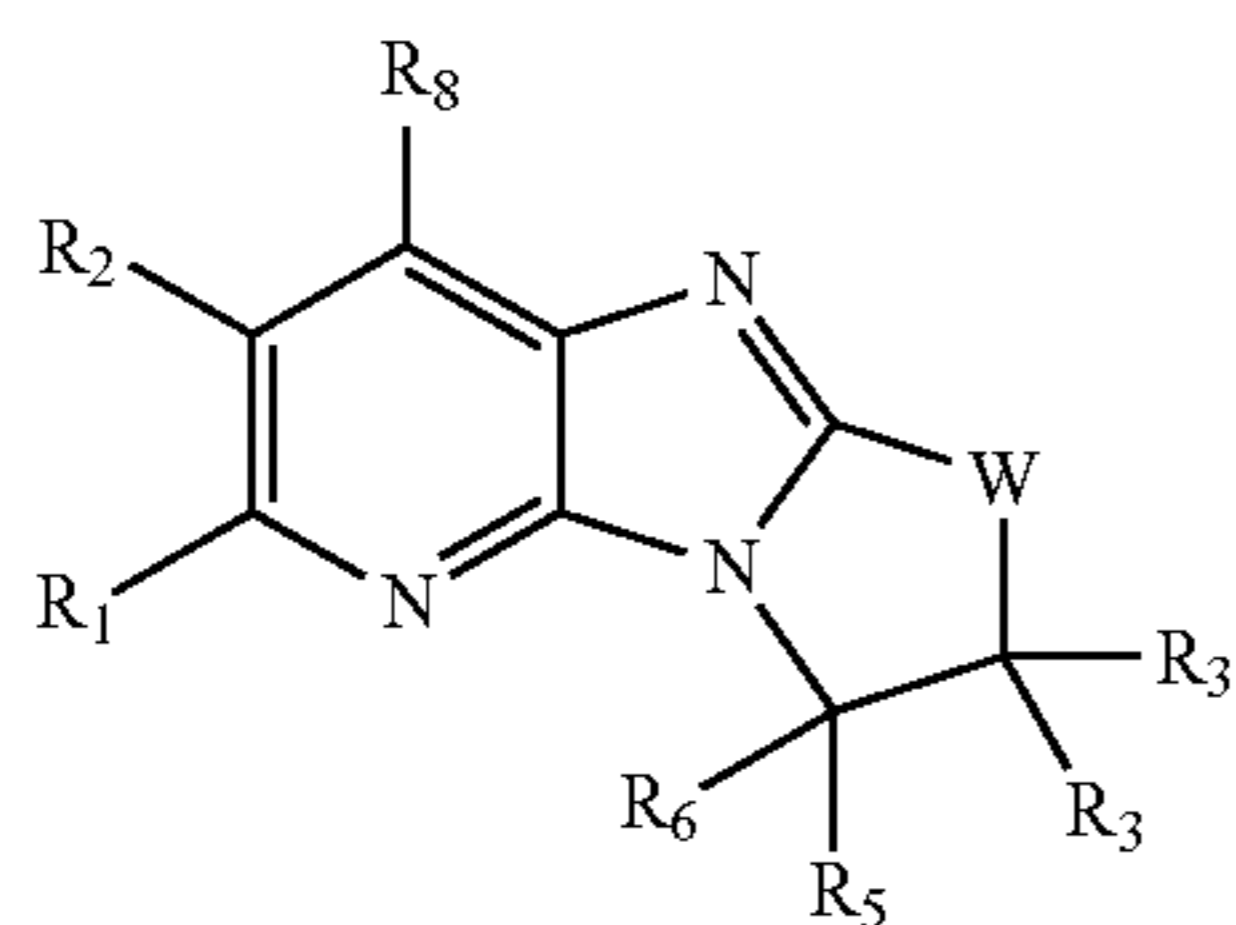
TABLE 5-continued

| Ex. No. | TNF induced HEK-Blue assay IC <sub>50</sub> value |
|---------|---|
| 13      | A (e1)<br>B (e2)<br>B (e3)<br>B (e4)              |
| 14      | B (e1)<br>A (e2)<br>B (e3)<br>A (e4)              |
| 15      | A (DM)<br>A (e1)<br>C (e2)<br>C (e4)              |
| 16      | A (DM)<br>A (e2)<br>C (e3)<br>A (e4)              |
| 17      | A (DM)  |
| 18      | B (DM)<br>A (e1)<br>C (e2)                        |
| 19      | B (e3)  |
| 20      | A (DM)  |
| 21      | A (e1)<br>B (e2)<br>B (e3)<br>A (e4)              |
| 22      | A (e1)<br>B (e2)<br>B (e3)<br>A (e4)              |
| 23      | A (e1)<br>B (e2)<br>A (e3)<br>A (e4)              |
| 24      | A (DM)<br>B (e1)<br>B (e2)<br>B (e3)<br>A (e4)    |
| 25      | A (rac)<br>A (e1)<br>A (e2)                       |
| 26      | A (rac)<br>A (e1)<br>C (e2)                       |
| 27      | A (rac)<br>A (e2)                                 |
| 28      | A (rac)   |
| 29      | B (rac)<br>B (e2)                                 |
| 30      | B (rac)<br>B (e2)                                 |
| 31      | A (e1)  |
| 32      | A (rac)<br>A (e1)<br>A (e2)                       |
| 33      | A (e1)<br>B (e2)                                  |
| 34      | A (rac)<br>A (e1)<br>B (e2)                       |
| 35      | B (rac)   |
| 36      | A   |
| 37      | A   |
| 38      | B   |
| 39      | B   |
| 40      | B   |



The invention claimed is:

1. A compound of Formula (I)



or a salt thereof, wherein:

X is N;

W is:

(i)  $-(CR_3R_3)_{1-4}-$ ;

(ii)  $-(CR_3R_3)_x-Y-(CR_3R_3)_y-$ ; or

(iii)  $-Y-(CR_3R_3)_2-Y-$ ;

each Y is independently O,  $NR_4$ , or  $S(O)_p$ ;

x is zero, 1, 2, or 3;

y is zero, 1, 2, or 3, provided that (x+y) is zero, 1, 2, or 3;

$R_1$  is H,  $R_{1a}$ ,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl substituted with zero to 6  $R_{1a}$ ,  $C_{2-6}$  alkynyl substituted with zero to 4  $R_{1a}$ ,  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_2$  is H, halo,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NO_2$ ,  $C_{1-6}$  alkyl substituted with zero to 6  $R_{1a}$ ,  $-(CR_gR_g)_rOR_e$ ,  $-(CR_gR_g)_rNR_cR_c$ ,  $-(CR_gR_g)_rS(O)_pR_b$ ,  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

each  $R_3$  is independently H, halo,  $-CN$ ,  $-OH$ ,  $-OCF_3$ ,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $-(CR_gR_g)_rC(O)R_b$ ,  $-(CR_gR_g)_rC(O)OR_b$ ,  $-(CR_gR_g)_rC(O)NR_cR_c$ ,  $-(CR_gR_g)_rOR_e$ ,  $-(CR_gR_g)_rOC(O)R_b$ ,  $-(CR_gR_g)_rOC(O)NR_cR_c$ ,  $-(CR_gR_g)_rOC(O)OR_d$ ,  $-(CR_gR_g)_rNR_cR_c$ ,  $-(CR_gR_g)_rNR_bC(O)R_d$ ,  $-(CR_gR_g)_rNR_bC(O)OR_d$ ,  $-(CR_gR_g)_rNR_bC(O)NR_cR_c$ ,  $-(CR_gR_g)_rNR_bS(O)_pR_d$ ,  $-(CR_gR_g)_rS(O)_pR_b$ ,  $-(CR_gR_g)_rS(O)_pNR_cR_c$ ,  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

each  $R_4$  is independently H,  $C_{1-6}$  alkyl substituted with zero to 6  $R_{1a}$ ,  $C_{3-7}$  cycloalkyl substituted with zero to 6  $R_{1a}$ ,  $-C(O)R_b$ ,  $-C(O)NR_cR_c$ ,  $-C(O)OR_b$ ,  $-S(O)_2R_b$ ,  $-S(O)_2NR_cR_c$ ,  $-S(O)_2OR_b$ ,  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-7 membered heterocyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (monocyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_5$  is  $-(CR_gR_g)_r$  (3-14 membered carbocyclyl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (aryl substituted with zero to 3  $R_{1a}$ ),  $-(CR_gR_g)_r$  (5-10 membered heterocyclyl

cyclyl substituted with zero to 3  $R_{1a}$ ), or  $-(CR_gR_g)_r$  (mono- or bicyclic heteroaryl substituted with zero to 3  $R_{1a}$ );

$R_6$  is H,  $C_{1-6}$  alkyl, or  $C_{1-6}$  haloalkyl;

or  $R_5$  and  $R_6$  together with the carbon atom to which they are attached form a 5- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring, each substituted with zero to 6  $R_{5a}$ ;

each  $R_{5a}$  is independently selected from H, halo,  $-CN$ ,  $-OH$ ,  $C_{1-3}$  alkyl,  $C_{1-3}$  fluoroalkyl, or  $C_{1-3}$  alkoxy; or two  $R_{5a}$  attached to neighboring carbon atoms of the spirocarbocyclic ring or the spiroheterocyclic ring, form a benzo ring along with the carbon atoms to which they are attached, said benzo substituted with zero to 4  $R_j$ ; or two  $R_{5a}$  attached to the same carbon atom of the spirocarbocyclic ring or the spiroheterocyclic ring, form  $=O$ ;

$R_8$  is H, halo,  $-CN$ ,  $C_{1-6}$  haloalkyl, or  $C_{1-3}$  alkoxy;

each  $R_{1a}$  is independently F, Cl,  $-CN$ ,  $C_{1-6}$  alkyl substituted with zero to 6  $R_a$ ,  $C_{3-6}$  cycloalkyl substituted with zero to 6  $R_a$ ,  $C_{1-3}$  alkoxy substituted with zero to 6  $R_a$ ,  $C_{1-3}$  haloalkoxy, heterocycloalkyl substituted with zero to 6  $R_a$ , aryl substituted with zero to 6  $R_a$ , mono- or bicyclic heteroaryl substituted with zero to 6  $R_a$ ,  $-C(O)R_b$ ,  $-C(O)OR_b$ ,  $-C(O)NR_cR_c$ ,  $-OC(O)R_b$ ,  $-OC(O)NR_cR_c$ ,  $-OC(O)OR_d$ ,  $-NR_cR_c$ ,  $-NR_bC(O)R_d$ ,  $-NR_bC(O)OR_d$ ,  $-NR_bS(O)_pR_d$ ,  $-NR_bC(O)NR_cR_c$ ,  $-NR_bS(O)_pNR_cR_c$ ,  $-S(O)_pR_b$ ,  $-S(O)_pNR_cR_c$ , or  $-C(O)NR_b(CH_2)_{1-3}NR_cR_c$ ;

each  $R_a$  is independently halo,  $-CN$ ,  $-OH$ ,  $-NO_2$ ,  $-NH_2$ ,  $C_{1-3}$  alkyl,  $C_{1-3}$  fluoroalkyl,  $C_{2-4}$  alkenyl,  $C_{2-4}$  alkynyl,  $C_{1-3}$  alkoxy,  $C_{1-3}$  fluoroalkoxy,  $-C(O)OH$ ,  $-C(O)(C_{1-3}$  alkyl),  $-C(O)O(C_{1-4}$  alkyl),  $-OC(O)(C_{1-3}$  alkyl),  $-NH(C_{1-3}$  alkyl),  $-N(C_{1-3}$  alkyl) $_2$ ,  $-C(O)NH(C_{1-3}$  alkyl),  $-OC(O)NH(C_{1-3}$  alkyl),  $-NHC(O)NH(C_{1-3}$  alkyl),  $-C(=NH)(NH_2)$ ,  $C_{3-7}$  carbocyclyl, aryl, 5-7 membered heterocyclyl, mono- or bicyclic heteroaryl,  $-O(aryl)$ ,  $-O(benzyl)$ ,  $-O(heterocyclyl)$ ,  $-S(C_{1-3}$  alkyl),  $-S(aryl)$ ,  $-S(heterocyclyl)$ ,  $-S(O)(aryl)$ ,  $-S(O)(heterocyclyl)$ ,  $S(O)_2(aryl)$ ,  $-S(O)_2(heterocyclyl)$ ,  $-NHS(O)_2(aryl)$ ,  $-NHS(O)_2(heterocyclyl)$ ,  $-NHS(O)_2NH(aryl)$ ,  $-NHS(O)_2NH(heterocyclyl)$ ,  $-NH(aryl)$ ,  $-NH(heterocyclyl)$ ,  $-NHC(O)(aryl)$ ,  $-NHC(O)(C_{1-3}$  alkyl),  $-NHC(O)(heterocyclyl)$ ,  $-OC(O)(aryl)$ ,  $-OC(O)(heterocyclyl)$ ,  $-NHC(O)NH(aryl)$ ,  $-NHC(O)NH(heterocyclyl)$ ,  $-OC(O)O(C_{1-3}$  alkyl),  $-OC(O)O(aryl)$ ,  $-OC(O)O(heterocyclyl)$ ,  $-OC(O)NH(aryl)$ ,  $-OC(O)NH(heterocyclyl)$ ,  $-NHC(O)O(aryl)$ ,  $-NHC(O)O(C_{1-3}$  alkyl),  $-C(O)NH(aryl)$ ,  $-C(O)NH(heterocyclyl)$ ,  $-C(O)O(aryl)$ ,  $-C(O)O(heterocyclyl)$ ,  $-N(C_{1-3}$  alkyl) $S(O)_2(aryl)$ ,  $-N(C_{1-3}$  alkyl) $S(O)_2(heterocyclyl)$ ,  $-N(C_{1-3}$  alkyl) $S(O)_2NH(aryl)$ ,  $-N(C_{1-3}$  alkyl) $S(O)_2NH(heterocyclyl)$ ,  $-N(C_{1-3}$  alkyl)(aryl),  $-N(C_{1-3}$  alkyl)(heterocyclyl),  $-N(C_{1-3}$  alkyl) $C(O)(aryl)$ ,  $-N(C_{1-3}$  alkyl) $C(O)(heterocyclyl)$ ,  $-N(C_{1-3}$  alkyl) $C(O)NH(aryl)$ ,  $-(CH_2)_{0-3}C(O)NH(heterocyclyl)$ ,  $-OC(O)N(C_{1-3}$  alkyl)(aryl),  $-OC(O)N(C_{1-3}$  alkyl)(heterocyclyl),  $-N(C_{1-3}$  alkyl) $C(O)O(aryl)$ ,  $-N(C_{1-3}$  alkyl) $C(O)O(heterocyclyl)$ ,  $-C(O)N(C_{1-3}$  alkyl)(aryl),  $-C(O)N(C_{1-3}$  alkyl)(heterocyclyl),  $-NHS(O)_2N(C_{1-3}$  alkyl)(aryl),  $-NHS(O)_2N(C_{1-3}$  alkyl)(heterocyclyl),  $-NHP(O)_2N(C_{1-3}$  alkyl)(aryl),  $-NHC(O)N(C_{1-3}$  alkyl)(aryl),  $-NHC(O)N(C_{1-3}$  alkyl)(heterocyclyl),  $-N(C_{1-3}$  alkyl) $S(O)_2N(C_{1-3}$  alkyl)(aryl),  $-N(C_{1-3}$  alkyl) $S(O)_2N(C_{1-3}$  alkyl)(heterocyclyl),  $-N(C_{1-3}$  alkyl) $C(O)N(C_{1-3}$



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alkyl)(aryl), —N(C<sub>1-3</sub> alkyl)C(O)N(C<sub>1-3</sub> alkyl)(heterocyclyl), or —Si(C<sub>1-3</sub> alkyl)<sub>3</sub>;

each R<sub>b</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>, heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl substituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>f</sub>;

each R<sub>c</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>, heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl substituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>f</sub>; or when attached to the same nitrogen, two R<sub>c</sub> along with the nitrogen atom to which they are attached form 4-8 membered heterocyclic ring optionally substituted with R<sub>g</sub>;

each R<sub>d</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>f</sub>, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>, heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl substituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>f</sub>;

each R<sub>e</sub> is independently H, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>f</sub>, C<sub>1-3</sub> haloalkyl, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>f</sub>, heterocycloalkyl substituted with zero to 6 R<sub>f</sub>, aryl substituted with zero to 3 R<sub>f</sub>, or mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>f</sub>;

each R<sub>f</sub> is independently H, halo, —OH, —CN, C<sub>1-6</sub> alkyl substituted with zero to 6 R<sub>a</sub>, C<sub>1-3</sub> alkoxy, C<sub>3-7</sub> cycloalkyl substituted with zero to 6 R<sub>a</sub>, heterocycloalkyl substituted with zero to 6 R<sub>a</sub>, aryl substituted with zero to 3 R<sub>a</sub>, or mono- or bicyclic heteroaryl substituted with zero to 3 R<sub>a</sub>;

each R<sub>g</sub> is independently H, F, —OH, —CN, C<sub>1-3</sub> alkyl, —CF<sub>3</sub>, or phenyl;

each p is independently zero, 1, or 2; and

each r is independently zero, 1, 2, 3, or 4.

2. The compound according to claim 1 or a salt thereof, wherein:

W is:

(i) —(CR<sub>3</sub>R<sub>3</sub>)<sub>1-3</sub>—; or

(ii) —(CR<sub>3</sub>R<sub>3</sub>)<sub>x</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>y</sub>—;

x is zero, 1, or 2;

y is zero, 1, or 2, provided that (x+y) is zero, 1, or 2;

R<sub>1</sub> is H, R<sub>1a</sub>, C<sub>1-3</sub> fluoroalkyl, C<sub>2-4</sub> alkenyl substituted with zero to 4 R<sub>1a</sub>, C<sub>2-4</sub> alkynyl substituted with zero to 3 R<sub>1a</sub>, —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-14 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(phenyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-7 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(monocyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>);

each R<sub>1a</sub> is independently F, Cl, —CN, C<sub>1-3</sub> alkyl substituted with zero to 4 R<sub>a</sub>, C<sub>3-6</sub> cycloalkyl substituted with zero to 4 R<sub>a</sub>, C<sub>1-2</sub> alkoxy substituted with zero to 3 R<sub>a</sub>, C<sub>1-2</sub> fluoroalkoxy, heterocycloalkyl substituted with zero to 3 R<sub>a</sub>, phenyl substituted with zero to 3 R<sub>a</sub>, or monocyclic heteroaryl substituted with zero to 3 R<sub>a</sub>;

each R<sub>a</sub> is independently F, Cl, Br, —CN, —OH, —NH<sub>2</sub>, —CHF<sub>2</sub>, or —CF<sub>3</sub>;

R<sub>2</sub> is H, F, Cl, Br, —CN, —CF<sub>3</sub>, —OCF<sub>3</sub>, C<sub>1-3</sub> alkyl substituted with zero to 4 R<sub>1a</sub>, or C<sub>3-6</sub> cycloalkyl substituted with zero to 4 R<sub>1a</sub>;

each R<sub>3</sub> is independently H, F, Cl, —CN, —OH, —OCF<sub>3</sub>, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> fluoroalkyl, or C<sub>2-3</sub> alkenyl;

R<sub>4</sub> is H, C<sub>1-3</sub> alkyl substituted with zero to 4 R<sub>1a</sub>, or C<sub>3-6</sub> cycloalkyl substituted with zero to 4 R<sub>1a</sub>;

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R<sub>5</sub> is —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(3-6 membered carbocyclyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(phenyl substituted with zero to 3 R<sub>1a</sub>), —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(5-10 membered heterocyclyl substituted with zero to 3 R<sub>1a</sub>), or —(CR<sub>g</sub>R<sub>g</sub>)<sub>r</sub>(monocyclic heteroaryl substituted with zero to 3 R<sub>1a</sub>);

R<sub>6</sub> is H, C<sub>1-3</sub> alkyl, or C<sub>1-3</sub> fluoroalkyl;

R<sub>8</sub> is H, F, Cl, Br, —CN, C<sub>1-3</sub> fluoroalkyl, or C<sub>1-3</sub> alkoxy; and

each r is independently zero, 1, or 2.

3. The compound according to claim 1 or a salt thereof, wherein:

W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>1-4</sub>—.

4. The compound according to claim 1 or a salt thereof, wherein:

W is —(CR<sub>3</sub>R<sub>3</sub>)<sub>x</sub>—Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>y</sub>—.

5. The compound according to claim 1 or a salt thereof, wherein:

W is —Y—(CR<sub>3</sub>R<sub>3</sub>)<sub>2</sub>—Y—.

6. The compound according to claim 1 or a salt thereof, wherein:

W is —CR<sub>3</sub>R<sub>3</sub>—;

R<sub>1</sub> is phenyl, pyrazolyl, pyridinyl, or pyrimidinyl, each substituted with zero to 1 substituents selected from —CH<sub>3</sub>, —C(CH<sub>3</sub>)<sub>2</sub>OH, —OCH<sub>3</sub>, morpholinyl, methylpiperazinyl, and carboxymethyl piperazinyl;

R<sub>2</sub> is H;

each R<sub>3</sub> is independently H, F, or —OH;

R<sub>5</sub> is phenyl substituted with zero to 2 substituents independently selected from F, —CH<sub>3</sub>, —CF<sub>3</sub>, —OCH<sub>3</sub>, —OCHF<sub>2</sub>, —OCF<sub>3</sub>, or cyclopropyl;

R<sub>6</sub> is H; and

R<sub>8</sub> is H.

7. The compound according to claim 1 or a salt thereof, wherein said compound is: 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (1); 8-(2-(difluoromethoxy)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (2); 8-(2-fluoro-6-(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (3); 8-2,5-dimethylphenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (4); 8-2,5-dimethylphenyl)-2-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (5); 8-(2,5-dimethylphenyl)-2-(2-morpholinopyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (6); 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-methyl-5-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (7); 8-(2,5-bis(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (8); 8-(2-cyclopropylphenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (9); 8-(2-(difluoromethoxy)phenyl)-2-(2-morpholinopyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (10); 8-(2-(difluoromethoxy)phenyl)-2-(2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (11); 2-(4-(2-hydroxypropan-2-yl)phenyl)-8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (12); 8-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-6-ol (13); 2-(4-(6-fluoro-8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (14); 2-(4-(8-(2-



(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (15); 2-(5-(8-(2-(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (16); 4-(5-(8-(2-(difluoromethoxy)phenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)morpholine (17); 8-(2-(difluoromethoxy)phenyl)-6-fluoro-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (18); 8-(2-(difluoromethoxy)phenyl)-6-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (19); 2-(5-(8-(2,5-dimethylphenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (20); 2-(4-(8-(2-cyclopropylphenyl)-6-fluoro-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (21); 2-(4-(6-fluoro-8-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (22); 2-(4-(6-fluoro-8-(2-fluoro-6-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (23); 2-(4-(6-fluoro-8-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (24); 2-(4-(8-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (25); 2-(4-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (26); 2-(5-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (27); 4-(5-(8-(2-(difluoromethoxy)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)morpholine (28); 8-(2-(difluoromethoxy)phenyl)-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (29); 8-(2-(difluoromethoxy)phenyl)-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (30); 2-(4-(8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (31); 2-(4-(8-(2-fluoro-6-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (32); 2-(4-(8-(2-cyclopropylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (33); 2-(4-(8-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (34); 2-(4-(5-(8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)piperazin-1-yl)acetic acid (35); (R)-2-(5-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (36); (R)-2-(4-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (37); (R)-8-(2,5-dimethylphenyl)-2-(4-(4-methylpiperazin-1-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (38); (R)-8-(2,5-dimethylphenyl)-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (39); or (R)-8-(2,5-dimethylphenyl)-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (40).

nyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (32); 2-(4-(8-(2-cyclopropylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (33); 2-(4-(8-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (34); 2-(4-(5-(8-(2-methoxyphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)piperazin-1-yl)acetic acid (35); (R)-2-(5-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)pyrimidin-2-yl)propan-2-ol (36); (R)-2-(4-(8-(2,5-dimethylphenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridin-2-yl)phenyl)propan-2-ol (37); (R)-8-(2,5-dimethylphenyl)-2-(4-(4-methylpiperazin-1-yl)phenyl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (38); (R)-8-(2,5-dimethylphenyl)-2-(6-methoxypyridin-3-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (39); or (R)-8-(2,5-dimethylphenyl)-2-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-6H-pyrrolo[2',1':2,3]imidazo[4,5-b]pyridine (40).

8. A pharmaceutical composition comprising one or more compounds according to claim 1 or a salt thereof; and a pharmaceutically acceptable carrier or diluent.

9. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically-effective amount of at least one compound according to claim 1, wherein said disease is an inflammatory or autoimmune disease selected from Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, cutaneous lupus, psoriasis, psoriatic arthritis, ankylosing spondylitis, cryopyrin-associated periodic syndromes, TNF receptor associated periodic syndrome, familial Mediterranean fever, adult onset stills, systemic onset juvenile idiopathic arthritis, multiple sclerosis, neuropathic pain, gout, and gouty arthritis.

\* \* \* \* \*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 10,189,840 B2  
APPLICATION NO. : 15/558692  
DATED : January 29, 2019  
INVENTOR(S) : Hai-Yun Xiao et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Column 2 (Abstract), Line 3, delete "Or" and insert -- or --, therefor.

In the Claims

Claim 1, Column 70, Lines 28-29, delete " $\text{---S(O)pNR}_c\text{R}_c$ ," and insert --  $\text{---S(O)pNR}_c\text{R}_c$ , --, therefor.

Claim 1, Column 70, Line 43, delete " $\text{---NH(aryl)}$ " and insert --  $\text{---NH(aryl)}$ , --, therefor.

Claim 2, Column 71, Line 49, delete " $\text{R}_{1a}\text{---}(\text{CR}_g\text{R}_g)_r(5-7)$ " and insert --  $\text{R}_{1a}, \text{---}(\text{CR}_g\text{R}_g)_r(5-7$  --, therefor.

Claim 7, Column 72, Line 41, delete "8-2,5-" and insert -- 8-(2,5- --, therefor.

Claim 7, Column 72, Lines 43-44, delete "8-2, 5-" and insert -- 8-(2,5- --, therefor.

Claim 7, Column 72, Line 48, delete "2-(4-2-hydroxypropan-2--1)" and insert -- 2-(4-(2-hydroxypropan-2-yl) --, therefor.

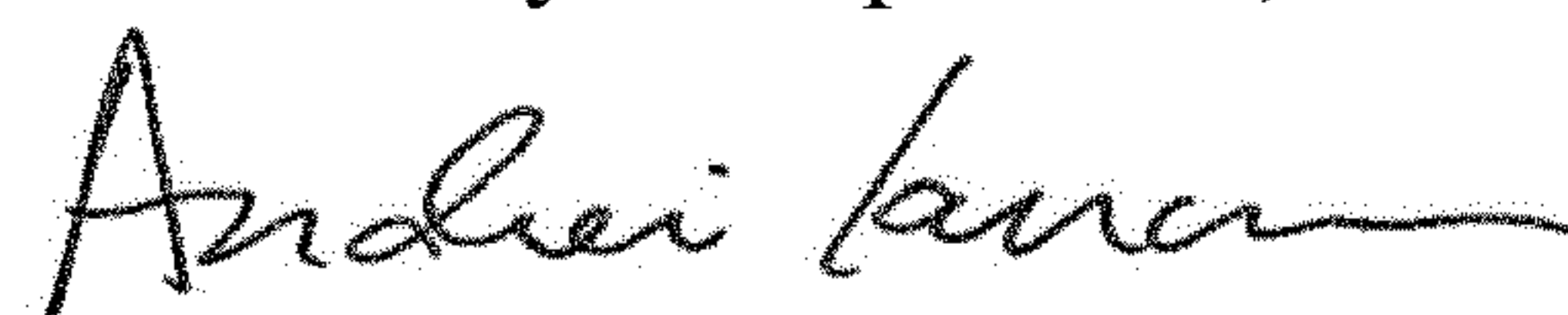
Claim 7, Column 72, Line 52, delete "-dihydro-6--pyrrolo [2',1':2,3]" and insert -- -dihydro-6H-pyrrolo[2',1':2,3] --, therefor.

Claim 7, Column 72, Line 57, delete "[4, 5-b]pyridin-6-ol(10);" and insert -- [4,5-b]pyridin-6-ol (10); --, therefor.

Claim 7, Column 72, Line 66, delete "[4, 5-b]" and insert -- [4,5-b] --, therefor.

Claim 7, Column 73, Line 10, delete "8-(2(difluoromethoxy))" and insert -- 8-(2-(difluoromethoxy) --, therefor.

Signed and Sealed this  
Tenth Day of September, 2019



Andrei Iancu  
Director of the United States Patent and Trademark Office



Claim 7, Column 73, Line 16, delete “-2yl)” and insert -- -2-yl) --, therefor.

Claim 7, Column 73, Line 22, delete “-2(trifluoromethyl)” and insert -- -2-(trifluoromethyl) --, therefor.

Claim 7, Column 73, Line 32, delete “[4, 5-b]” and insert -- [4,5-b] --, therefor.

Claim 7, Column 73, Lines 36-37, delete “[4, 5-b]” and insert -- [4,5-b] --, therefor.

Claim 7, Column 74, Line 14, delete “[4, 5-b]” and insert -- [4,5-b] --, therefor.

Claim 7, Column 74, Lines 15-16, delete “-(4methylpiperazin-” and insert -- -(4-methylpiperazin- --, therefor.